PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE (PADAC) Meeting

June 11, 2015

FDA Briefing Document

BLA 125526: Mepolizumab for injection for the add–on maintenance treatment in patients 12 years and older with severe eosinophilic asthma as identified by blood eosinophils greater than or equal 150 cells/microliter at initiation of treatment or greater than equal to 300 cells/microliter in the past 12 months.

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the biologics licensing application (BLA) 125526, mepolizumab for injection for the add-on maintenance treatment in patients 12 years and older with severe eosinophilic asthma as identified by blood eosinophils greater than or equal 150 cells/microliter at initiation of treatment or greater than equal to 300 cells/microliter in the past 12 months to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FDA Briefing Package

DIVISION MEMORANDUM

Date: May 14, 2015

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To: Members, Pulmonary-Allergy Drugs Advisory Committee (PADAC)

Subject: Overview of the FDA background materials for the New Biologics License application (BLA) 125526, for Nucala® (mepolizumab) for Injection for the proposed indication of "add-on maintenance treatment in patients aged 12 years and older with severe eosinophilic asthma identified by blood eosinophils greater than or equal to 150 cells/µL at initiation of treatment or blood eosinophils greater than or equal to 300 cells/µL in the past 12 months. Nucala has been shown to reduce exacerbations of asthma in patients with an exacerbation history."

I. Introduction

Thank you for your participation in the upcoming Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on June 11, 2015. As members of the FDA Advisory Committee, we consider your expert scientific advice and recommendations to the FDA very important to our regulatory decision making processes. The objective of the upcoming meeting is to discuss the new biologics licensing application (BLA) 125526 from GlaxoSmithKline (GSK) for Nucala® (mepolizumab) for Injection for add-on maintenance treatment of asthma in patients 12 years of age and older with severe eosinophilic asthma proposed by GSK to be identified by blood eosinophils greater than or equal to 150 cells/µL at initiation of treatment or blood eosinophils greater than or equal to 300 cells/µL in the past 12 months. The proposed dosage and administration is 100 mg administered subcutaneously (SC) once every 4 weeks.

Mepolizumab is a humanized monoclonal antibody (IgG1, Kappa, mAb) to human interleukin 5 (IL-5). While several cytokines can affect eosinophils, interleukin 5 is the main cytokine involved in the regulation of blood and tissue eosinophils.[1] Nucala® (mepolizumab) for Injection is not currently marketed in the United States or any other country in the world. If approved for the treatment of asthma, mepolizumab will be the first monoclonal antibody to IL-5 to be approved in the United States for any indication. Mepolizumab acts by preventing IL-5

[1] Tavernier J, Plaetinck G, Guisez Y, Van der Heyden J, Kips J, Peleman R, Devos R. The role of IL-5 in the production and function of eosinophils. In: Whetton AD, Gordon JR, editros. Cell biochemistry. Vol. 7: Hematopoietic cell growth factors and their receptors. New York: Plenum Press: 2000.p. 321-361.

from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. This action inhibits IL-5 signaling and the over-expression of peripheral blood and tissue eosinophils.[2]

Asthma is a chronic inflammatory disorder of the airways affecting more than 22 million persons in the United States. Asthma remains the most common chronic disease of childhood and can have significant impact at the individual and societal level. In spite of the therapeutic advances in the management and treatment of asthma, challenges remain in many areas.[3] There are several classes of products available for use in patients with persistent asthma. These include inhaled corticosteroids (ICS), inhaled long-acting beta-adrenergic agents (LABAs), leukotriene modifying drugs, methylxanthines, and the monoclonal antibody to IgE known as omalizumab. While several products are approved for long-term maintenance treatment of asthma, there are no therapies approved specifically for a subset of patients with severe asthma and predefined eosinophil levels. With the appreciation that asthma is a chronic inflammatory disorder, inhaled corticosteroids have become the cornerstone of maintenance therapy for patients with persistent asthma. In spite of these available therapies, there are patients who remain poorly controlled on maximum therapy (including oral corticosteroids) and there are patients with severe persistent asthma who are resistant to corticosteroids.[4] There is ongoing research in the area of severe persistent asthma to better understand the heterogeneity that exists in this subgroup and some results from this ongoing research and updated guidelines on severe asthma have been described in the literature.[5,6] Patients with severe persistent asthma are at risk for more frequent asthma exacerbations and hospitalizations due to asthma and therefore development of therapies to control asthma in this subpopulation is an important therapeutic step in improving asthma outcomes.

In early clinical studies in mild asthmatics, mepolizumab was shown to decrease eosinophils in blood, bone marrow, and bronchial mucosa.[7] However, initial studies in patients with moderate asthma did not show a benefit in clinical outcomes. The clinical program conducted to support this BLA was carried out in patients with severe persistent asthma after preliminary proof-of-concept studies in a more severe population suggested that there was potential benefit of mepolizumab in a severe asthma population.

The content of this document and the materials prepared by the Agency reflect the preliminary findings and opinions based on review of the information submitted by GSK to support this BLA

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[2] GSK Clinical Overview

[3] National Asthma Education and Prevention Report (NAEPP) Expert Panel Report 3- Guidelines for the Diagnosis and Management of Asthma. At: https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines

[4] Donald Y.M. Leung, and Stanley J. Szefler. Diagnosis and management of steroid-resistant asthma. Clin Chest Med. 1997 Sep; 18 (3): 611-625

[5] Moore WC., Meyers DA., Wenzel SE., et.al Identification of asthma phenotypes using cluster analysis in the severe asthma research program. Am J Respir and Crit Care Med Vol 181: pp 313-323, 2010

[6] Kian Fan Chung, Wenzel SE., Brozek JL., Bush A., et.al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Task Force Report ERS/ATS Guidelines on Severe Asthma. At: https://www.thoracic.org/statements/resources/allergy-asthma/Severe-Asthma-CPG-ERJ.pdf

[7] Study SB-240563/036 “A Double Blind, Placebo Controlled, Parallel Group Study to Assess the Effect of 750 mg SB-240563 (Anti-IL-5) on Clinical Features, Cutaneous Late-Phase Reactions and Bronchial, Nasal, Skin, Bone Marrow and Blood Eosinophils in Male and Female Patients with Atopic Asthma” -GSK BLA 125-526 sequence 0000 November 4, 2014.

but does not represent the Agency's final position. The feedback and insight you will provide to us at this advisory committee meeting will be an important factor in our decision on this application. Attached are the background materials for this meeting. In addition to this memorandum, the FDA background materials include the following: Draft questions/issues for discussion, Clinical and Statistical Briefing Document, and Clinical Pharmacology Briefing Document.

II. Regulatory History of Mepolizumab Development in Asthma

The Investigational New Drug (IND) application for mepolizumab was opened in 1997 and the first randomized, placebo-controlled efficacy and safety study was conducted in 1999 in patients with moderate asthma. Efficacy was assessed by pulmonary function and symptoms and although mepolizumab treatment resulted in a profound decrease in blood eosinophils, mepolizumab treatment did not demonstrate a clinical benefit in that patient population.[8] GSK had ongoing interactions with the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) regarding a clinical development program for a targeted asthma population in advice meetings in February 2006, and April 2009. An End-of Phase 2 meeting was held in May 2012 and the Division provided additional advice in July and December 2012. GSK was advised that the patient population selected for the development program should be one that could be adequately described in product labeling and reflective of a population readily identifiable in the real-world. Dose ranging, adequacy of the safety database, and justification for the proposed restriction of the product to a specific subset of asthma patients were discussed. A pre-BLA meeting was held in January 2014 and the content and format of the BLA, presentation of the data, adequacy of the dose-ranging and dose selection, and adequacy of long-term data were discussed. The Division also pointed out that GSK should provide justification in the BLA to support the proposed restriction of mepolizumab to a subset of severe asthma patients based on eosinophil levels.

III. Product Information

Mepolizumab is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells and has a molecular weight of approximately 149 kDa. Nucala® (mepolizumab) for Injection is supplied as a sterile, preservative-free lyophilized powder for reconstitution and subcutaneous (SC) injection in single-use glass vials. Upon reconstitution with Sterile Water for Injection, each single-use vial delivers 100 mg of mepolizumab in 1 mL, 160 mg sucrose/mL, 7.14 mg sodium phosphate dibasic heptahydrate/mL, and 0.67 mg/mL polysorbate 80 with a pH of 7.0.

[8] Study SB 240563/006: A Multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the safety and efficacy of intravenous SB 240563 (250 mg and 750 mg) in patients with asthma. [trial period 2/1999 – 10/1999] GSK BLA 125-526 sequence 0000 November 4, 2014.

IV. Overview of the Mepolizumab Clinical Program for Severe Persistent Asthma

As with all asthma development programs, dose and dosing regimen are important considerations. GSK explored both the intravenous (IV) and subcutaneous (SC) routes of administration in the earlier development of mepolizumab. For the selection of the dose and route of administration for the severe asthma program, GSK conducted one dose ranging study (study 97) in patients with severe refractory asthma that explored multiple doses using the IV route of administration and one pharmcodynamic study which was used to bridge the IV and SC routes of administration using a pharmacodynamic endpoint (reduction in blood eosinophil levels). The dose-ranging study 97 also served as an efficacy study. The table below outlines the dose-ranging and pivotal efficacy [and safety] studies that were submitted to support the BLA.

Table 1: Clinical Dose-Ranging and Efficacy Studies (Study SB240563/006 not shown)

ID **Trial period (yr.)** **(Total enrolled)**	**Number of U.S. subjects (% of study population)**	**Study Characteristics** **-Subject age** **-Subject characteristics** **-Study design, objective** **-Study duration**	**Treatment groups** **(N§)**	**Primary efficacy endpoint**
		Dose-ranging/dose selection studies		
MEA112997* 11/2009 -12/2011 (616)	78 (13%)	-12 to 65 yr. -Severe refractory asthma with markers of eosinophilic inflammation** -Randomized, DB, PC -52 weeks	Mepo 75 mg IV (n =153) Mepo 250 mg IV (n=152) Mepo 750 mg IV (n=156) Placebo (n =155)	§§Rate of asthma exacerbations
MEA114092¶ 02/2011 – 03/2012 (70)	5 (7%)	-18 to 65 yr. -History of asthma on stable dose of current meds for 12 weeks prior to screening -Blood eosinophilia > 300 µL within 12 months or > 200 µL at screening -Open-label -12 weeks	Mepo 12.5 mg SC (n =21) Mepo 125 mg SC (n = 15) Mepo 250 mg SC (n =23) Mepo 75 mg IV (n = 11)	Pharmacodynamic endpoint – blood eosinophil levels
		Pivotal Efficacy Studies		
MEA115588 10/2012 -01/2014 (576)	67 (12%)	-At least 12 yr. and minimum weight of 45 kg -Severe refractory asthma with markers of eosinophilic inflammation** -Randomized, DB, PC, DD -32 weeks	Mepo 75 mg IV (n = 191) Mepo 100 mg SC (n = 194) Placebo (n = 191)	§§Rate of asthma exacerbations
115575 10/2012 -12/2013 (135)	7 (5%)	-At least 12 yr. and minimum weight of 45 kg -Severe refractory asthma with markers of eosinophilic inflammation** -Randomized, DB, PC - 24 weeks	Mepo 100 mg SC (n = 69) Placebo SC (n = 66)	Percent reduction of OCS dose during weeks 20 - 24

Study ID shown as GSK study number. Studies are identified by the last 2 numbers (underlined) in this memo.
Trial Period= month/year study started to month/year study completed
DB = double-blind, DD = double-dummy, PC = placebo-controlled
Mepo = mepolizumab
*Study **97** is also an efficacy study
**Markers of eosinophilic inflammation defined as follows:

For study **97:** blood eosinophils ≥ 300/µL **or** sputum eosinophils ≥3% **or** exhaled nitric oxide ≥ 50 ppb **or** deterioration of asthma control following a ≤25% reduction in regular maintenance dose of ICS in the previous 12 months. For study **88** and **75**: Blood eosinophil count of ≥300µ/L that is related to asthma in the past 12 months or ≥ 150/µL at Visit 1 (study 88) or between Visit 1 and Visit 3 (study 75). ¶ Study **92** provide pharmcodynamic data to bridge IV and SC route of administration and support for 100 mg SC dose selection OCS: oral corticosteroid **§** N = Intent-to-treat; **§§** GSK used "frequency" but "rate" is more appropriate term from statistical standpoint

Dose Selection

Studies 97 and 92 provided evidence to support the selection of the 100 mg SC dose of mepolizumab for further evaluation in pivotal efficacy studies. In study 97, subjects received mepolizumab 75, 250, or 750 mg or placebo IV once every four weeks to Week 48 for a 52-week treatment period. Additional details about this study will be discussed below with the discussion of the pivotal efficacy studies. In study 92, subjects received 12.5, 125, or 250 mg of mepolizumab SC, or 75 mg IV once every 4 weeks for a total of 3 doses. Results of study 97 showed that treatment with all 3 doses of mepolizumab resulted in a statistically significant reduction in exacerbations compared to placebo and there was no significant treatment difference among the three doses. In study 92, a dose-dependent decrease in blood eosinophil levels was observed in all treatment groups by the third day post-treatment with similar reductions seen for 125 mg SC exposure and 75 mg IV exposure. These data, along with model-estimated inhibition of blood eosinophils provided support for evaluating both 100 mg SC and 75 mg IV in the pivotal phase 3 exacerbation study, Study 88. Importantly, similar treatment effects were seen in Study 88 providing evidence that the data from the 75 mg IV dose can be applied to the 100 mg SC dose. The data from these three studies support the conclusion that mepolizumab 75 mg IV and 100 mg SC would provide similar efficacy. The proposed dose for marketing is 100 mg SC. IL-5 levels were measured in both studies and consistent with the mechanism of action of mepolizumab, total IL-5 levels [undetectable at baseline] were measurable with mepolizumab treatment and reach saturation points in both studies with no evidence of a dose response.

Mepolizumab Pivotal Clinical Studies

Characteristics of Enrolled Subjects

Some demographic and baseline characteristics of the subjects enrolled in the dose-ranging/ efficacy and pivotal clinical studies that form the basis of support for this BLA are shown in Table 2. The inclusion criteria are consistent with criteria that would characterize patients as having severe asthma by the most recent severe asthma guidelines.[9] In two of the studies (97 and 88) criteria specific to those defined in the 2000 ATS workshop on refractory asthma were required.[10] All trials used criteria deemed to be indicative of eosinophilic inflammation to select subjects for inclusion in the studies (see Table 1).

[9] Kian Fan Chung, Wenzel SE., Brozek JL., Bush A., et.al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Task Force Report ERS/ATS Guidelines on Severe Asthma. At: https://www.thoracic.org/statements/resources/allergy-asthma/Severe-Asthma-CPG-ERJ.

[10] American Thoracic Society: Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. Am j Respir Crit Care Med 162 (6): 2314-2351 2000

****Table 2: Baseline Characteristics and Demographics of the Subjects in the Pivotal Efficacy Clinical Studies and the Dose-Ranging/Efficacy Study**

Parameter	**Study 97 N = 616**	**Study 88 N = 576**	**Study 75 N = 135**
Mean age (yrs.) (range)	47 (15-74)	50 (12-82)	50 (16-74)
Female (%)	63	57	55
Males (%)	37	43	45
BMI ((mean) (range))	28.5 (17-52)	27.77 (16.1 -49.7)	28.6 (19.7 -52.1)
Smoking history (% never smoked)	78	72	82
Parameter	**Study 97 N =616**	**Study 88 N = 576**	**Study 75 N =135**
Duration of asthma (yrs.) mean, median	19 (14.3)	20 (17.0)	19 (16.0)
>2 exacerbations in prior yr. (%)	54	43	51
¶Prebronchodilator FEV_1 [(mean % predicted) [min-max]]	58 [19-118]	61 [18-128]	59 [15 -94]
Prebronchodilator FEV1/FVC ((mean) (SD))	0.63 (0.14)	0.64 (0.13)	0.62 (0.12)
§% Reversibility at screening, ((mean) (SD))	25 (21.8)	28 (22.6)	24 (18.9)
ΩBaseline eosinophil count µL (SD)	384 (368)	445 (429)	377 (339)
¶Prebronchodilator FEV_1 value at screening for study 97, at baseline for study 88, and at Week 0 for study 75 §Lung function (% improvement in FEV_1) post short-acting bronchodilator treatment			
ΩSource: Reviewer programs exacerbation forest plots subgr s 97 20150406.sas, exac forest plots subgr s88 20150417.sas, ocs subgr s75201503			
**Source: GSK submission: Study 97 CSR Tables 8, 5.15, 518; Study 88 CSR Tables 6, 7,8,9 and Study 75 CSR Table 9, 10, 12, 13			

There was a higher percentage of females (59%) in the development program and the mean age of the study population was 49 years. Not shown in the table is the breakdown of the population by age, but it is worth noting that adolescents (12 – 17 years) were underrepresented in this program. There were only 26 adolescent patients in the entire development program. Also not shown in the table is the distribution of the study population by race. The majority of subjects were white and minorities made up less than 10% of the overall population and the overall percentage of subjects of African descent was ~ 3%. [See Clinical and Statistical Briefing Document Table 26].

Study Design

All studies were randomized, placebo-controlled, parallel group studies. Study 88 included a double-dummy design to maintain the blind as this study evaluated both the IV and SC routes of administration. Subjects in study 97 and 88 were required to be on background maintenance therapy with high dose ICS for the prior 12 months (with or without oral corticosteroids [OCS]) plus an additional controller (LABA, leukotriene inhibitor, or theophylline). Subjects in study 75 were required to be on regular treatment with maintenance systemic corticosteroids (5 to 35 mg/day of prednisone or equivalent) and high-dose ICS in the 6 months prior to screening in addition to being on an additional controller medication. Subjects enrolled in study 97 and 88 were required to have a history of two (2) or more exacerbations in the prior year, whereas, subjects in study 75 were not required to have a history of exacerbations. This is a reasonable exception as all subjects in study 75 were on continuous OCS.

The primary efficacy endpoint in studies 97 and 88 was the rate of asthma exacerbations. Asthma exacerbation was defined using criteria consistent with the ATS/ERS definition for asthma exacerbation.[11] Study 97 and 88 differed in the duration of treatment. Subjects were treated once every 4 weeks through week 48 for a treatment duration of 52 weeks in study 97, whereas, subjects were treated once every 4 weeks with the last dose given at week 28 for a total of 32 weeks of treatment in study 88.

The primary efficacy endpoint for study 75 was the percent reduction of OCS dose at week 24 compared to the baseline dose. Study 75 had a 24-week treatment period and was designed with four (4) study periods: i) an initial oral corticosteroid optimization period of 3-10 weeks duration where subjects' oral corticosteroid dose was titrated in a scheduled manner to ensure that subjects entered the double-blind treatment period on the lowest OCS dose that controlled their symptoms; ii) an induction phase of 4 weeks duration where the subjects received their first dose of blinded investigational treatment and their OCS dose was maintained; iii) the OCS reduction phase (weeks 4 to 20) when the OCS dose was reduced every 4 weeks as long as asthma control was maintained; iv) the maintenance phase (weeks 20 – 24) where no further reductions in OCS dose were made.

Secondary efficacy measures in study 97 and 88 include time to first exacerbation, rate of exacerbations requiring hospitalizations, FEV_1 (mean change from baseline over the treatment period), assessment of asthma control using the Asthma control questionnaire (ACQ) score and health-related quality of life questionnaires (AQLQ, SGRQ), and blood and sputum [sputum in study 97 only] eosinophil levels. Secondary efficacy endpoints evaluated in study 75 include various measures of OCS reduction during weeks 20-24 while maintaining asthma control (i.e. proportion of subjects who achieve: i) a 50% or greater reduction in their daily OCS dose; ii) total reduction in their OCS dose; iii) reduction of OCS dose to ≤ 5 mg), rate of asthma exacerbations, asthma exacerbations requiring hospitalizations, health-related quality of life using the SGRQ, and mean change from baseline in FEV_1 at week 24.

Efficacy Results

Results of the primary efficacy findings for study 97 and 88 are shown in Table 3

Table 3: Primary Efficacy Results Study 97 and Study 88

Study	Treatment in mg	N	Annual rate of asthma exacerbation	Difference to placebo	Rate Ratio* (95% CI)
97	Mepolizumab 75 mg IV	153	1.24	-1.16	0.52 (0.39, 0.69)
	Mepolizumab 250 mg IV	152	1.46	-0.94	0.61 (0.46, 0.81)
	Mepolizumab 750 mg IV	156	1.15	-1.24	0.48 (0.36, 0.64)
	Placebo	155	2.40	---	
88	Mepolizumab 75 mg IV	191	0.93	-0.81	0.53 (0.40, 0.72)
	Mepolizumab 100 mg SC	194	0.83	-0.92	0.47 (0.35, 0.64)
	Placebo	191	1.74	----	
*p<0.001 for each dose group compared to placebo					

[11] Reddel, Helen K., et al. "An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice." Am J Respir and Crit Care Med 180.1 (2009): 59-99.

Study	Treatment in mg	N	Annual rate of asthma exacerbation	Difference to placebo	Rate Ratio* (95% CI)
Data Source: Clinical and Statistical Briefing Document Table 12					

A statistically significant reduction in asthma exacerbations in all mepolizumab treatment arms was seen in both studies. There was no significant benefit of doses higher than 75 mg IV over that of the 75 mg IV dose in study 97 and there was no significant difference in exacerbation benefit between the mepolizumab 75 mg IV dose and the 100 mg SC dose in study 88. The rate of exacerbations requiring hospitalizations or ER visit was lower in the mepolizumab treatment groups compared to placebo, but the overall rates of exacerbations requiring hospitalizations or ER visits were low across the treatment groups (shown below in Table 4).

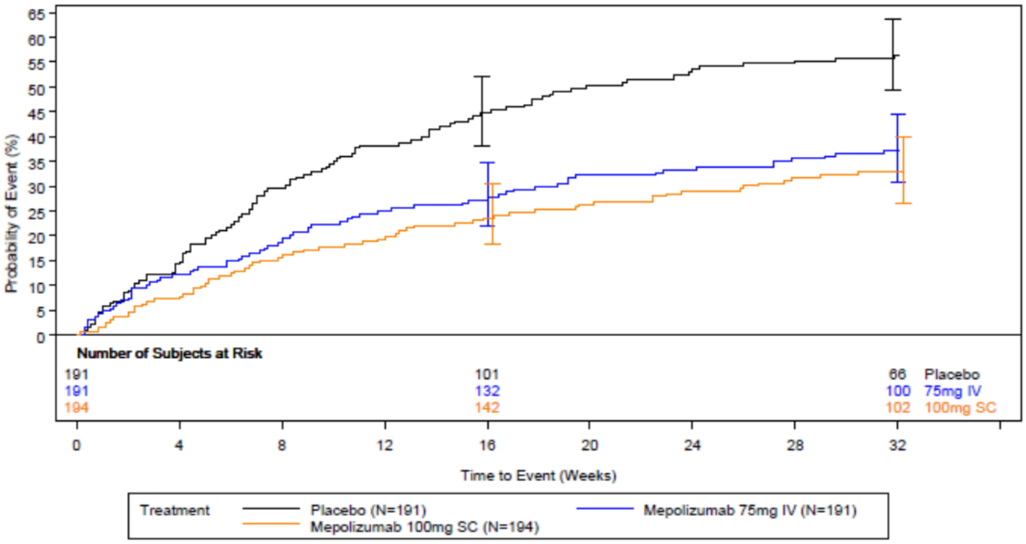
Table 4: Exacerbations Requiring Hospitalizations or ER Visits

Study	Treatment in mg	N	Annualized rate of exacerbation requiring hospitalization or ER visit	Annualized rate of exacerbations requiring hospitalization	Rate Ratio (95% CI) exacerbations requiring hospitalization or ER visit	Rate Ratio* (95% CI) exacerbations requiring hospitalization
97	Mepo 75 mg IV	153	0.17	0.11	0.40 (0.19, 0.81) ¶	0.61 (0.28, 1.33)
	Mepo 250 mg IV	152	0.25	0.12	0.58 (0.30, 1.12)	0.65 (0.31, 1.39)
	Mepo 750 IV	156	0.22	0.07	0.52 (0.27, 1.02)	0.37 (0.16, 0.88) ¶
	Placebo	155	0.43	0.18		
88	Mepo 75 IV	191	0.14	0.06	0.68 (0.33, 1.41)	0.61 (0.23, 1.66)
	Mepo 100 SC	194	0.08	0.03	0.39 (0.18, 0.83)	0.31 (0.11, 0.91) ¶
	Placebo	191	0.20	0.10		

¶True p-value is >0.05 for dose compared to placebo
Data Source: Joint Clinical and Statistical Review Table 15 and Reviewer program exac studies 88 97 2015 04 17.sas

Another important assessment in exacerbation studies is the time to first exacerbation. In both studies 97 and 88, mepolizumab-treated subjects had an increased time to first exacerbation. The Kaplan-Meier plot below shows the incidence curve for time to first exacerbation in Study 88. A similar trend was seen in study 97.

Figure 1: Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation: Study 88



Source: GSK Study 88 CSR Figure 4

With regards to lung function (FEV_1), given the proposed mechanism of mepolizumab, it is not anticipated that the product would have a significant bronchodilator effect. Nevertheless, evaluation of lung function is an important part of any asthma development program as deterioration of lung function would be an unacceptable trade-off for other potential benefits. Change from baseline in pre-bronchodilator FEV_1 at Week 52 (study 97) and Week 32 (Study 88) were evaluated as secondary endpoints. In both studies a small numerical improvement over placebo was seen with mepolizumab treatment. In study 97 the change was 61 mL (CI -39,161) for the 75 mg IV dose compared to placebo at Week 52. The improvement was 100 mL (CI: 13,187) in study 88 (at Week 32) for the 100 mg SC dose [See Clinical and Statistical Briefing Document Figures 13, 14].

In study 75, mepolizumab treatment resulted in a significant reduction in OCS use. The baseline mean OCS (mg) use was similar in the two treatment groups 13.2 mg in the placebo group and 12.4 in the mepolizumab group. The OCS reduction results are shown in Table 5.

Table 5: OCS Reduction during Weeks 20-24 in Study 75

	Placebo **N =66**	**Mepolizumab** **N = 69**
Categorized percent reduction from baseline in OCS during weeks 20-24	Frequency (percent)	Frequency (percent)
90% -100%	7(11)	16 (23)
75% to < 90%	5 (8)	12 (17)
50% to <75%	10 (15)	9 (13)
>0% - < 50%	7 (11)	7 (10)
No decrease in OCS, lack of asthma control, or withdrawal from treatment	37 (56)	25 (36)
Odds ratio 95% CI p-value		2.39 (1.25,4.56) P = 0.008

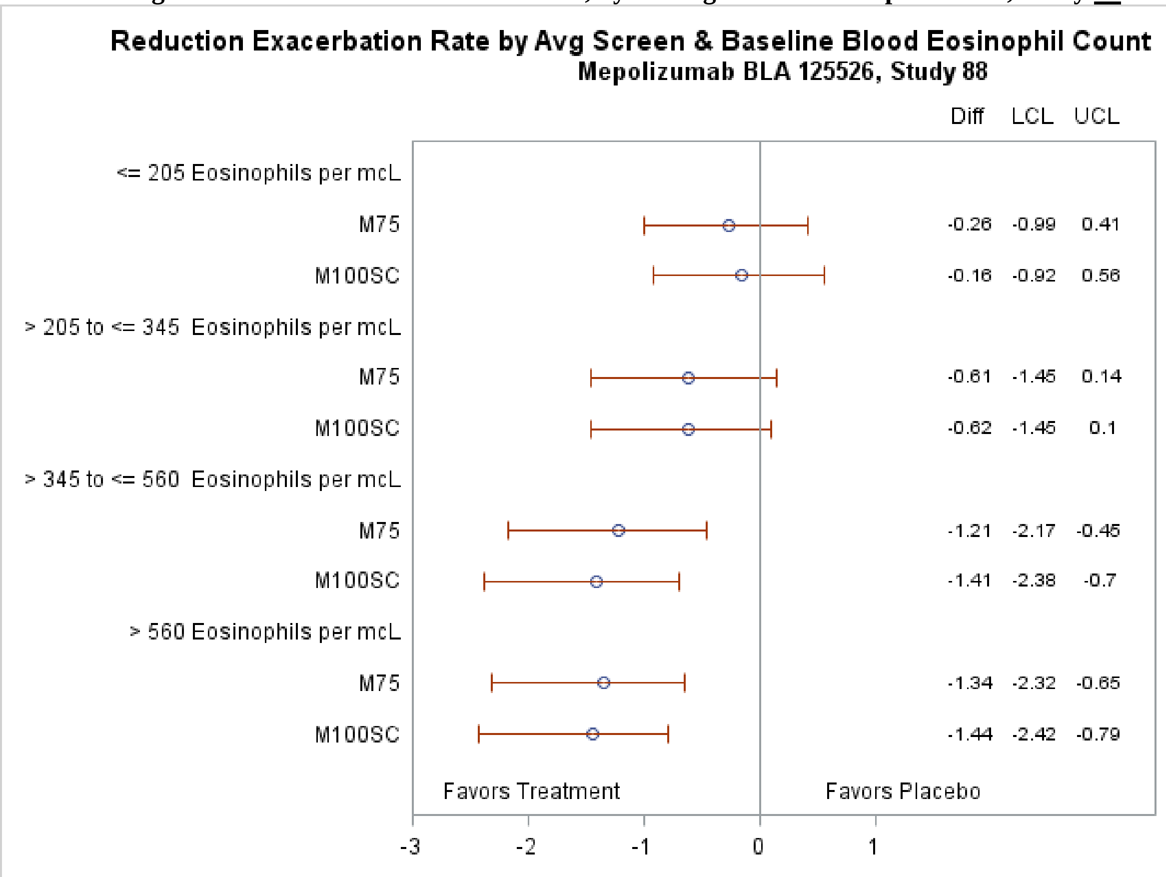
Source: GSK Study 75 CSR Table 16

Subjects treated with mepolizumab were able to achieve a greater percent reduction from baseline OCS dose while maintaining asthma control compared to subjects in the placebo arm. The frequency of exacerbations was evaluated in study 75 and showed a favorable trend for the mepolizumab treatment. However, this outcome was included in the study as an "other" endpoint without an adjustment for multiplicity. Similar to what was seen in study 88, there was a numerical improvement in FEV_1 of ~ 100 mL from baseline at Week 24 in study 75.

Health-related quality of life using the St Georges Respiratory Questionnaire (SGRQ) was assessed in studies 88 and 75. In both studies, the mepolizumab treatment group achieved an improvement in the Total Score that exceeded the Minimal Clinical Important Difference (MCID) of 4. In one of the studies (Study 88), the placebo group also achieved an improvement from baseline in the Total Score that exceeded the MCID of 4 points (9). Statistical issues regarding multiplicity aside, it is unclear how one would interpret the clinical meaningfulness of the change seen in the mepolizumab treatment arm when the placebo group also experienced a clinically meaningful improvement. The change seen in these 2 studies is unusually large compared to what has been seen in COPD programs where this questionnaire is more frequently used. Asthma control assessed with the ACQ also showed a favorable numerical trend [See Clinical Briefing Document Table 23].

From secondary exploratory analyses, the treatment effect of mepolizumab as shown in Figure 2 appears to be greater in patients with higher blood eosinophil levels. Whether a specific eosinophil level should dictate use of mepolizumab in this patient population with severe persistent asthma and a history of frequent exacerbations would be an important topic for discussion by the Advisory Committee. The question of whether mepolizumab treatment would be beneficial in patients who would have otherwise met the degree of asthma severity for enrollment in these studies but who may not meet the blood eosinophil study entry criterion that was pre-specified for these studies, cannot be definitively answered from the data in this program as data from patients with these characteristics are limited.

Figure 2: Exacerbation Rate Reductions, by Average Blood Eosinophil Count, Study 88



Source: FDA Statistical Reviewer Analysis

Mepolizumab review of safety

In addition to the safety data from the placebo-controlled efficacy studies outlined in Table1, additional long term safety data are available from two ongoing open label studies with mepolizumab. Study MEA115666 (n =347) is an open-label extension (OLE) study of study 97 and study MEA115661 (n=651) is an open-label extension of studies 88 and 75. The dose of mepolizumab in both OLE studies is the dose proposed for marketing (100 mg SC every 4 weeks). While the safety database is relatively small compared to databases of other asthma development programs, it is a reasonable size database considering that this program is not designed to support the full spectrum of asthma severity but rather, a subpopulation of asthmatics.

In addition to the usual safety assessments in clinical studies such as adverse event recording, vital signs, physical examination, and clinical laboratory measures, GSK implemented a prospective cardiovascular monitoring strategy in studies 88 and 75 to evaluate for potential cardiovascular signals. This intensive monitoring was driven by the observation of an imbalance in serious adverse events in the cardiovascular system class (SOC) in the high dose (intravenous) mepolizumab group in study 97. The cardiovascular monitoring strategy included an

Independent data Monitoring Committee and external adjudication panel to review the cardiovascular safety. Given that the product is a biologic for injection, events of special interest such as hypersensitivity reactions, anaphylaxis, local site reactions, opportunistic infections, malignancies and immunogenicity were assessed throughout the development program.

Deaths, SAEs, dropouts and discontinuations

There were a total of five (5) deaths reported in the controlled efficacy and safety studies and one (1) death in the ongoing OLE studies. The number of deaths is unusual as the occurrence of deaths in an asthma development program is rarely seen. Two of the deaths were in placebo-treated subjects, 2 occurred in the mepolizumab 250 mg IV group, and one occurred in the 750 mepolizumab IV group and one occurred in a subject on mepolizumab 100 mg SC (in the open label study). Three of the deaths were respiratory-related deaths. There does not appear to be any relationship with mepolizumab, nevertheless, the number of deaths is unusual for an asthma program. [See Clinical and Statistical Briefing Document Table 31].

Events leading to dropouts and discontinuations did not raise any new safety concerns. There were no safety concerns for a cardiovascular safety signal from the safety data. [See Clinical and Statistical Briefing Document Tables 32-39].

Common Adverse Events

Common adverse events (occurring in ≥ 3% of subjects in a given treatment group) that were seen in the mepolizumab 100 mg SC treatment group included headache, injection site reaction, back pain, fatigue, influenza, urinary tract infection, abdominal pain upper, pruritus, eczema, and muscle spasms. The safety findings for the common adverse events did not show a dose response upon review of the common adverse events with the other doses of mepolizumab in the controlled efficacy/safety studies or in the data from the ongoing OLE studies through the October 27, 2014 safety cutoff date. [See Clinical and Statistical Briefing Document Section 6.4.1, Table 43]

Adverse Events of special interest, Malignancies, Laboratory findings and Immunogenicity

There was an increase in local injection site reactions in the mepolizumab 100 mg SC treatment group compared to placebo in the controlled clinical studies database. Hypersensitivity reactions [exposure adjusted values] were higher for the 250 mg and 750 mg IV mepolizumab dose compared to placebo. For the 100 mg SC dose, (the dose proposed for marketing) hypersensitivity reactions occurred at a lower frequency compared to placebo. There was one potential case of anaphylaxis but this case is confounded by a prior history of sulfite allergy and exposure to sulfite [See Clinical and Statistical Briefing Document Section 6.3.4 and Table 40].

Herpes zoster was reported in both the controlled studies and the ongoing open label extension studies. In addition, 3 reports of esophageal candidiasis were reported in the open label studies through the October 27, 2014 cutoff date. The development program excluded patients with parasitic disease and lingering concerns remain about the use of this product in persons who may be exposed to parasitic infections. There was one report of parasitic gastroenteritis in one subject receiving mepolizumab 100 mg SC in Study 88, but no cases of parasitic infection has been reported from the open label extension studies through the safety cutoff date. [See Clinical and Statistical Briefing Document Section 6.3.4, Table 41].

There were no treatment-related imbalances in malignancies in the controlled studies (3 malignancies in placebo-treated subjects and 2 in mepolizumab-treated subjects). Up to the safety cutoff date, a total of 10 malignancies have been reported. [See Clinical and Statistical Briefing Document Table 42].

Other than the expected decrease in blood eosinophils, there were no concerning findings in the laboratory measures and immunogenicity assessments did not raise any safety concerns.

V. Risk-Benefit of Mepolizumab in Severe Persistent Asthma and Issues for Consideration

Mepolizumab was originally evaluated in patients with moderate asthma and the results from that early product development suggested that mepolizumab was not beneficial across the broad spectrum of asthma severity. The development program in a severe asthma population appears to be successful using a clinically relevant endpoint (i.e. exacerbations).

The submitted data show consistent effect for reduction in exacerbations in a severe persistent asthma population enriched with markers of eosinophilic inflammation and with a history of frequent exacerbations despite high dose inhaled corticosteroids and other controller therapies. In addition, the data show that a significant number of subjects who were on continuous oral corticosteroids were able to reduce their dose of OCS. Time to first exacerbation, and exacerbations due to hospitalization and/or ER visits all showed a favorable trend for mepolizumab- treated subjects. Multiple doses were explored in the dose-ranging study and there was no appreciable efficacy advantage of higher doses. Evaluation of both SC and IV routes of administration in study 88 along with the efficacy results from study 75 [in which the 100 mg SC dose was evaluated] together with the pharmacodynamic (study 92) and dose-ranging (study 97) data, provide adequate support for the selection of the 100 mg SC dose proposed for marketing. Change in FEV_1 from baseline showed a consistent favorable trend in all the studies. While the actual change was small in comparison with the lung function benefit seen with bronchodilators, this improvement is on a background of ICS/LABA treatment in the majority (>93%) of the subjects. Measures of asthma control using the ACQ also appear to be supportive of the benefit of mepolizumab in the population studied.

In addition to the overall discussion regarding the adequacy of the efficacy and safety data to support approval of mepolizumab, there are additional issues for which we are seeking advisory committee input.

An important consideration for approval of any product is the identification of the patient population most likely to benefit from use of the product. GSK's severe asthma development program sought to incorporate patient selection criteria to allow enrollment of subjects most likely to demonstrate a treatment benefit. Except for study 75 [where subjects were required to be on continuous OCS], all subjects were required to have a history of at least 2 exacerbations despite being on high dose ICS and other controller therapies. This exacerbation history is consistent with a severe persistent asthma population as defined in current guidelines.[12] While exacerbation history was not an explicit entry criterion in study 75, these patients would have also met the criteria for severe persistent asthma by virtue of being on continuous OCS for > 6 months of the year. The additional criteria of eosinophilic inflammation defined by GSK further enriched the studies for a population most likely to respond favorably to treatment with mepolizumab and secondary exploratory analyses suggest a greater treatment effect of mepolizumab with higher eosinophil levels.

Whether the observations in this development program are sufficient to understand the efficacy of mepolizumab in a patient population with asthma severity consistent with that of the population studied in the mepolizumab program but who do not meet the eosinophilic inflammation requirements and/or to delineate categorical cutoffs for eosinophil levels to define such a subset of the severe asthma population are issues for discussion at the advisory committee meeting. Given the labile nature of eosinophil counts and the effect of corticosteroids on eosinophils, as well as the limited data in subjects with lower eosinophil levels in this development program, the role of this laboratory measure as the deciding factor in whether or not to use mepolizumab in a severe persistent asthma population with a history of exacerbations remains unclear.

Mepolizumab is proposed for patients 12 years of age and older. However, there is limited data in the adolescent (12 -17 years) population. The mean age of the study population was 49 years and there were only 26 adolescents enrolled in the entire program and of these 16 were exposed to mepolizumab. With such limited representation of adolescents in the program conclusions regarding efficacy and safety are quite challenging.

Finally, the data in the African-American/African descent population are also very limited. In the entire program there were only 40 (3%) subjects of African descent across studies 97 and 88. There were no subjects of African-American/African descent in study 75 [although there were 5 study sites in the U.S]. Historically, the racial distribution in asthma programs has been predominately White with minorities making up a very small percentage of the study population. However, in this severe asthma program the percentage of African-Americans/African descent is even smaller. Given the severity of disease in the patient population proposed for this product and the increased asthma morbidity and mortality reported in asthmatic patients of African-American/African descent,[13, 14]the representation of African-Americans in any severe asthma program would be an important topic for discussion.

[12] Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-373.ERS/ATS document
[13] Jean G. Ford, Lee McCaffrey. Understanding disparities in asthma outcomes among African Americans. Clin Chest med 27 (2006) 423-430
[14] Nelson DA, Johnson CC, Divine GW, et.al. Ethnic differences in the prevalence of asthma in middle class children. Ann Allergy Asthma Immunol 1997; 78:21-6

Draft Topics for Discussion

1. Discuss the efficacy data for mepolizumab 100 mg SC administered once every 4 weeks to support its use in the treatment of severe persistent asthma. Consider the following issues in the discussion:
    a) asthma severity of the patient population most likely to benefit from treatment with mepolizumab
    b) role of eosinophils in determining initiation of treatment with mepolizumab
    c) adequacy of the efficacy data in children 12 to 17 years of age
    d) ethnicity of the study population

2. Do the efficacy data provide substantial evidence of a clinically meaningful benefit of mepolizumab 100 mg SC once every 4 weeks for the treatment of severe persistent asthma?

    a) in adults, 18 years of age and older?
    If no, what further data should be obtained?

    b) in children 12 – 17 years of age/
    If no, what further data should be obtained?

3. Discuss the safety data for mepolizumab 100 mg SC administered once every 4 weeks. Include in your discussion: size of the overall database and adequacy of the safety data in children 12 to 17 years of age.

4. Has the safety of mepolizumab 100 mg SC administered once every 4 weeks been adequately demonstrated for treatment of patients with severe asthma?

    a) In adults 18 years and older?
    If not what further data should be obtained?

    b) In children 12 – 17 years of age?
    If not, what further data should be obtained?

5. Do the available efficacy and safety data support approval of mepolizumab 100 mg SC administered once every 4 weeks for the treatment of patients with severe persistent asthma?

    a) in adults 18 years of age and older
    If not what further data should be obtained?

    b) in children 12 – 17 years of age
    If not what further data should be obtained?

Joint Clinical and Statistical Briefing Document for the Pulmonary—Allergy Drugs Advisory Committee Meeting

June 11, 2015

Nucala® (mepolizumab for injection) BLA 125526

Dose: 100 mg subcutaneous injection every 4 weeks

Proposed indication:
"Add–on maintenance treatment in patients 12 years and older with severe eosinophilic asthma identified by blood eosinophils ≥ 150 cells/μL at initiation of treatment or ≥ 300 cells/μL in the past 12 months. Nucala has been shown to reduce exacerbations of asthma in patients with an exacerbation history."

Reviewers: Sofia Chaudhry, MD, Medical Officer
Robert Abugov, Ph.D., Statistical Reviewer

Department of Health & Human Services
Food & Drug Administration
Center for Drug Evaluation & Research
Division of Pulmonary, Allergy and Rheumatology Products
Silver Spring, MD 20993

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List of Abbreviations

ACQ	Asthma control questionnaire
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse event of special interest
ATS	American Thoracic Society
AQLQ	Asthma quality of life questionnaire
DB	Double blind
DD	Double dummy
CV	Cardiovascular
CSR	Complete study report
ED	Emergency department
Eos	Eosinophils
ER	Emergency room
ERS	European Respiratory Society
FENO	Fractional exhaled Nitric Oxide
FEV1	Forced expiratory volume in one second
FP	Fluticasone propionate
MC	Multicenter
Mepo	Mepolizumab
ICS	Inhaled corticosteroids
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
LABA	Long acting beta agonist
LFT	Liver function test
LTRA	Leukotriene receptor antagonist
PC	Placebo-controlled
PCSA	Placebo-controlled severe asthma database
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred term
OCS	Oral corticosteroids
OLE	Open label extension
R	Randomized
SAE	Serious Adverse Event
SGRQ	St. George’s Respiratory Questionnaire
SOC	System Organ Class

1 Executive Summary

GlaxoSmithKline (GSK) has submitted a Biologics Licensing Application (BLA) in support of mepolizumab, a first-in-class, anti-interleukin 5 monoclonal antibody (anti-IL-5), as a treatment for asthma. The dose proposed for marketing is 100 mg subcutaneous every 4 weeks. The proposed indication specifies use of the product as add-on maintenance therapy in patients 12 years of age and older with severe eosinophilic asthma as identified by blood eosinophils ≥ 150 cells/μL at initiation of treatment or ≥ 300 cells/μL in the past 12 months.

Three pivotal efficacy and safety studies have been submitted by GSK in support of this application. These include a 52-week dose-ranging and exacerbation study (Study 97), a 32-week exacerbation study (Study 88) and a steroid reduction study (Study 75). All three studies enrolled a population of severe asthmatics consistent with the criteria outlined in the recently published ATS/ERS Severe Asthma Guidelines[1]. In addition, the primary endpoint, the annualized rate of asthma exacerbations, used a definition consistent with the ATS/ERS criteria[2]. The primary endpoint in Study 75 evaluated the reduction in oral corticosteroid dose without loss of asthma control.

The populations were further enriched for patients with evidence of “airway eosinophilic inflammation”, although it is notable that the criteria used to identify eosinophilic inflammation differed between the two exacerbation studies. In Study 97, multiple inclusion criteria[3] were used to identify these patients, while Studies 88 and 75 utilized specific peripheral blood eosinophil thresholds of ≥ 150 cells/μL at the time of treatment initiation or 300 cells/μL in the past 12 months. Notably, due to the design of the program, the data evaluating use of the product in a broader population of severe asthmatics who fail to meet the eosinophilic inflammation criteria, and specifically the peripheral blood eosinophil thresholds applied in the phase 3 program are limited.

The 100 mg subcutaneous (SC) dose and route proposed for marketing are supported by the lack of differential dose-response seen in Study 97, similar treatment effects of the 75 mg IV and 100 mg SC dose in Study 88 and supporting PK/PD IV to SC bridging data from Study 92.

Efficacy of the product is supported by data from the two exacerbation studies, both of which demonstrate a statistically significant reduction in the annualized rate of

[1] Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-373.
[2] Reddel, Helen K., et al. "An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice." American journal of respiratory and critical care medicine 180.1 (2009): 59-99.
[3] Peripheral blood eosinophil count ≥ 300 cells/μl in past 12 months, sputum eosinophil count > 3%, FENO > 50, or rapid loss of asthma control following 50% reduction in steroid dose.

exacerbations for all evaluated mepolizumab treatment arms compared to placebo. The oral steroid reduction study provides additional efficacy support for the 100 mg SC dose by demonstrating a statistically significant reduction in oral corticosteroid dose compared to placebo without loss of asthma control.

Given the uniqueness of the targeted patient population and to gain a better understanding on the modification of the mepolizumab treatment effect by peripheral blood eosinophil counts, both the sponsor and the Agency conducted multiple exploratory analyses of the data from this development program. These exploratory analyses demonstrate a strong trend towards an increased mepolizumab treatment effect as peripheral blood eosinophil count increases.

The safety database for the product is primarily composed of data from the three efficacy and safety studies in addition to longer-term safety data provided by two open-label extension studies. Lingering concerns remain over mepolizumab use and the risk of parasitic disease; however, no major safety signals have emerged from a review of the safety data.

This Advisory Committee panel will be asked to discuss the available efficacy and safety data and the risk/benefit profile for use of mepolizumab in the intended population. In addition, the panel will be asked to discuss how the data from this clinical development program should be applied in clinical practice to inform appropriate use of the product in the severe asthmatics and whether the observations from this development program are sufficient to delineate a new subset of asthma. The heterogeneity of severe asthma, absence of clinical guidelines defining severe "eosinophilic" asthma, and the underlying lability of peripheral blood eosinophil measurements will be important considerations in the panel's discussion.

The Agency is also requesting a discussion on the adequacy of the data in patients of African American/African Heritage descent given the limited enrollment of these patients in this global clinical development program and increased disease burden that is seen in this population[4].

The panel will also be asked to discuss the adequacy of the adolescent data to support approval of the product given the limited amount of available data from which to draw conclusions and unknown existence of the targeted patient population in a pediatric population. As an approval of this product would trigger the Pediatric Research Equity Act (PREA), the Agency has regulatory authority to require additional studies in the pediatric population. To that end, the panel is asked to discuss whether additional evaluation in pediatric patients is warranted and requests a discussion of the appropriate ages to study including the youngest age to evaluate.

[4] SilverS, Stacy K., and David M. Lang. "Asthma in African Americans: What can we do about the higher rates of disease?." Cleveland Clinic journal of medicine 79.3 (2012): 193-201.

2 Introduction and Regulatory Background

2.1 Product Information

This Biologics Licensing Application (BLA) is submitted in support of mepolizumab at a dose of 100 mg by subcutaneous injection every 4 weeks for the add-on maintenance treatment in patients 12 years and older with severe eosinophilic asthma identified by blood eosinophils ≥ 150 cells/μL at initiation of treatment or ≥ 300 cells/μL in the past 12 months.

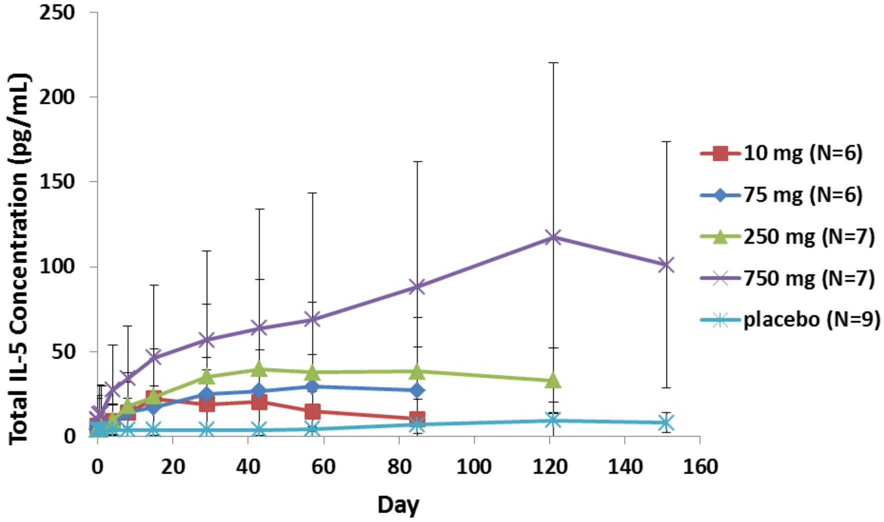
Mepolizumab is a humanized monoclonal antibody (IgG1 kappa) targeting interleukin-5 (IL-5) and is produced by recombinant DNA technology in Chinese hamster ovary cells. It is a sterile, lyophilized powder for injection. Following reconstitution with Sterile Water for Injection, USP, each single-use vial will deliver 100 mg/ml mepolizumab in 1 mL, 160 mg/mL sucrose, 7.14 mg/mL sodium phosphate dibasic heptahydrate, and 0.67 mg/mL polysorbate 80, with a pH of 7.0.

2.2 Pharmacodynamics

Mepolizumab is a humanized monoclonal antibody (IgG1 kappa) targeting interleukin-5 (IL-5). IL-5 is a cytokine important in the growth, differentiation, activation and survival of eosinophils.

In a single-dose study in healthy Japanese males, mepolizumab treatment demonstrated an increase in total serum IL-5 levels in a dose-dependent fashion. Total IL-5 levels were largely unchanged in the placebo group, and free IL-5 levels were essentially undetectable with or without mepolizumab treatment (Figure 1).

Figure 1: Mean (± SE) serum total IL-5 concentrations in healthy Japanese males: Study 05

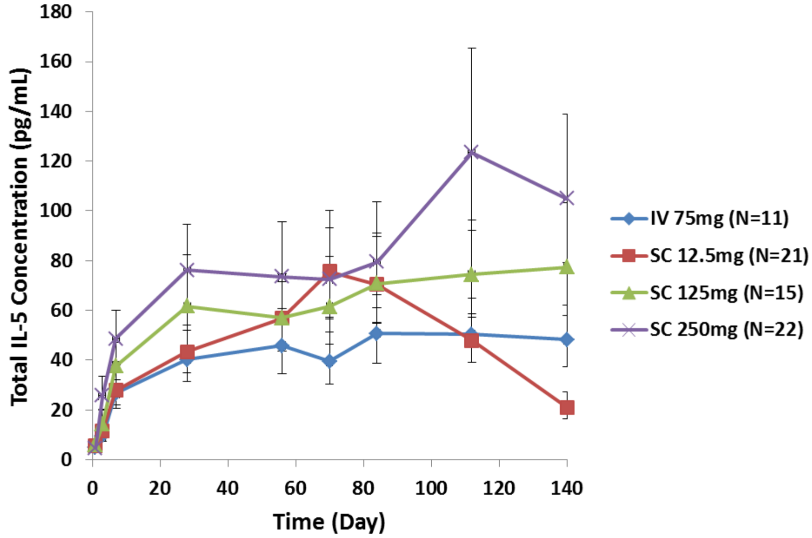


Source: Clinical Pharmacology Briefing Document Figure 4

To support its proposed subcutaneous dosing, the sponsor conducted a pharmacokinetic/pharmacodynamic (PK/PD) IV to SC study (Study 92), a multicenter, open-label, dose-ranging study to determine the PK and PD of mepolizumab administered intravenously or subcutaneously to adult asthmatic subjects with elevated blood eosinophil levels. Subjects were randomized to one of four treatment arms: 12.5 mg SC, 125 mg SC, 250 mg SC or 75 mg IV. Each treatment was administered every 4 weeks for a total of 3 doses. Blood samples for safety, PD, PK, biomarkers and immunogenicity analyses were assessed. A total of 66 subjects completed the study.

In Study 92, an increase in total IL-5 levels was seen following mepolizumab treatment; however, a dose-response relationship was not clearly demonstrated. This study did not include a placebo arm (Figure 2).

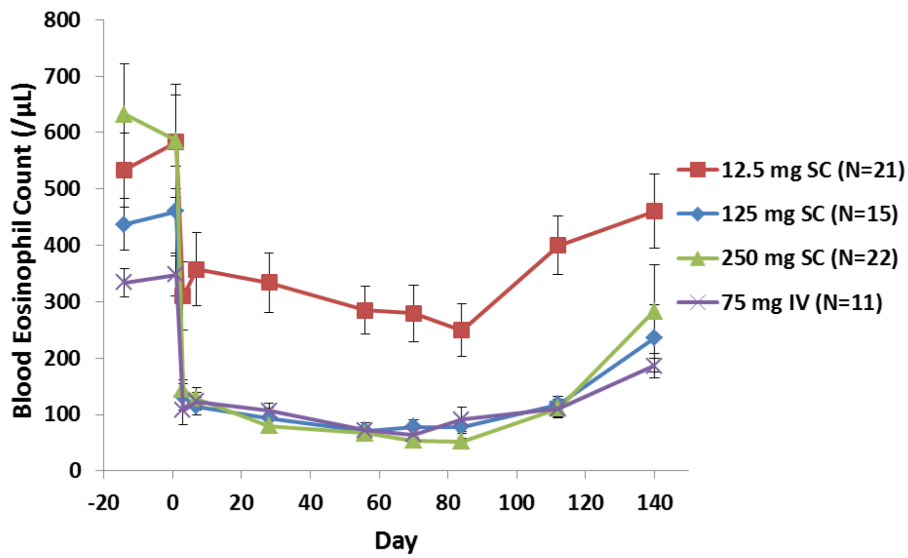
Figure 2: Mean (± SE) serum total IL-5 concentrations: Study 92



Source: Clinical Pharmacology Briefing Document: Figure 5

A reduction was seen in blood eosinophil levels in a dose dependent fashion with greater treatment effect noted for doses > 12.5 mg SC every 4 weeks (Figure 3).

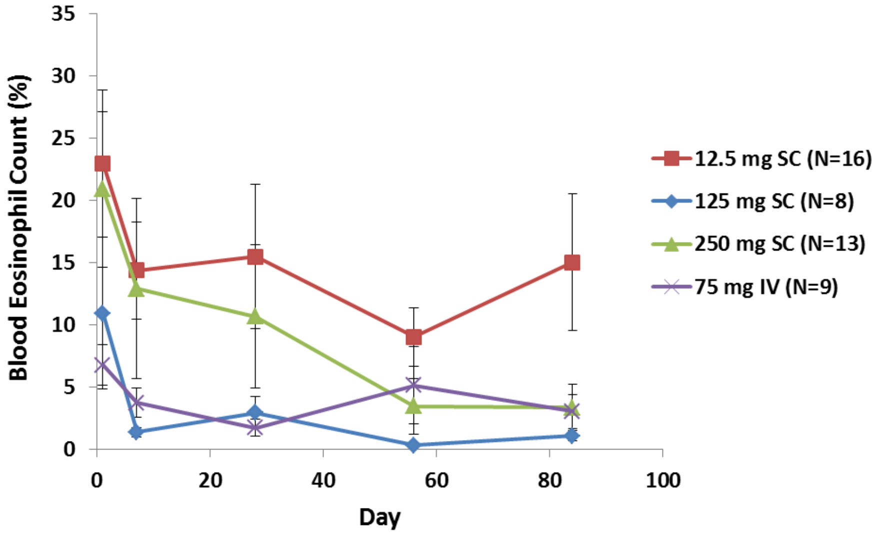
Figure 3: Mean (± SE) absolute blood eosinophil counts over time: Study 92



Source: Clinical Pharmacology Briefing Document: Figure 1

There was a general trend towards a reduction in sputum eosinophil counts following mepolizumab treatment in Study 92 (Figure 4). However, the sputum eosinophil counts (%) at baseline (pre-dose on Day 1) were not balanced between four active treatment groups. The largest decrease from baseline was observed in the mepolizumab 250 mg SC groups, with smaller decreases in the mepolizumab12.5 mg SC group.

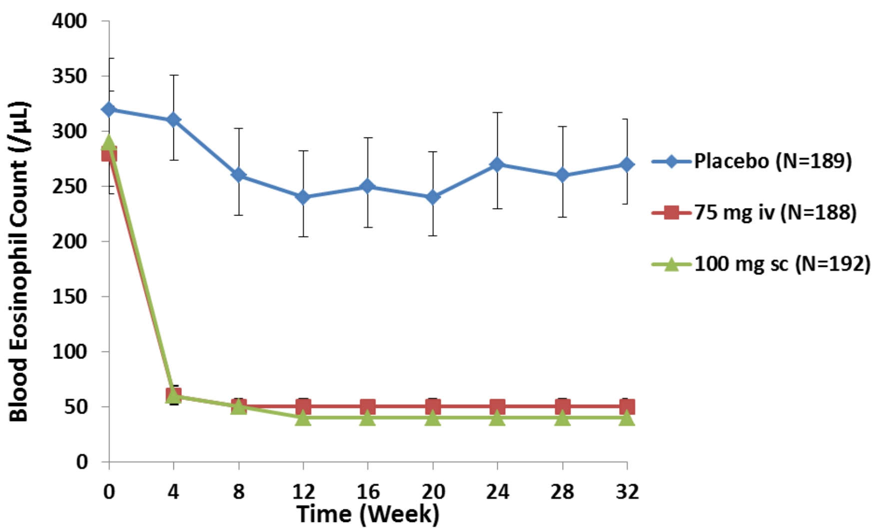
Figure 4: Mean (± SE) sputum eosinophil counts (%) over time: Study 92



Source: Clinical Pharmacology Briefing Document: Figure 3

In Study 88, following 100 mg SC mepolizumab treatment every four weeks for 32 weeks, blood eosinophils demonstrated an 86% decrease from baseline for mepolizumab treated subjects compared to a 16% decrease by placebo. The plateau phase of blood eosinophil reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period (Figure 5).

Figure 5: Mean (± SE) absolute blood eosinophil counts over time: Study 88



Source: Clinical Pharmacology Briefing Document: Figure 2

2.3 Clinical Background

Asthma is a chronic inflammatory disorder of the airways, the diagnosis and management of which are outlined in several consensus documents (National Asthma Education and Prevention Program. Expert Panel Report 3: guidelines for the diagnosis and management of asthma[5] [NAEPP EPR3 report] and the Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention, 2013[6] [GINA guidelines]).

While the majority of patients are successfully managed with a step-wise treatment approach, a subset of patients remains uncontrolled despite maximal medical management. Initial efforts to establish criteria defining a "severe refractory asthma" phenotype were published in 1999/2000[7,8] with updated guidelines defining a "severe asthma" phenotype published more recently (International ERS/ATS Severe Asthma guidelines[9]).

The International ERS/ATS guidelines define severe asthma as patients with a confirmed asthma diagnosis which requires treatments with high dose inhaled corticosteroids (ICS) plus LABA or leukotriene modifier/theophylline[10] therapy to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy. Additionally, the guidelines outline that patients who do not meet the aforementioned criteria, but whose asthma worsens when corticosteroids are tapered, also meet the definition of severe asthma.

In these guidelines, "uncontrolled asthma" is defined as meeting any of the four following criteria:

- Poor symptom control: ACQ consistently > 1.5 or ACT < 20 (or "not well controlled" by NAEPP or GINA guidelines) over 3 months of evaluation
- Frequent severe exacerbations: 2 or more bursts of systemic corticosteroids (>3 days each) in the previous year

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[5] National Institutes of Health (NIH). National Heart, Lung, and Blood Institute (NHLBI).National Asthma Education and Prevention Program. Expert Panel Report 3: guidelines for the diagnosis and management of asthma. August 2007. NIH publication no. 07-4051.
[6] Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention, 2013. Website accessed April 28,2015: http://www.ginasthma.org/.
[7] Chung KF, et al. "Difficult/therapy resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy Resistant Asthma. European Respiratory Society" Eur Respir J 1999: 13(5): 1198-1208.
[8] "Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions." American Thoracic Society. Am J Respir Crit Care Med 2000: 162(6): 2341-2351.
[9] Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-373.
[10] and/or systemic corticosteroids for ≥ 50% of the previous year

- Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year
- Airflow limitation: FEV1 <80% predicated (in the presence of a reduced FEV1/FVC) with both short- and long-acting bronchodilators withheld

Beyond categorizing asthma by severity, there is an active body of research working to identify additional asthma phenotypes and endotypes using various biomarkers. One approach was conducted by the Severe Asthma Research Program (SARP) which employed statistical modeling to identify asthma clusters. While 5 subgroups were identified, overlap between the groups was seen with respect to identifying biomarkers[11]. This overlap exemplifies the heterogeneity seen within asthma and difficulties with further sub-classification of the disease. While alternative approaches have outlined, to date, there are no consensus guidelines outlining the identification or management of specific asthma subgroups.

2.4 Currently Available Treatments for Proposed Indication

There are no treatments specifically approved for the treatment of severe asthma with characteristic peripheral blood eosinophil levels in the United States. However, oral corticosteroids are typically used in clinical practice to treat asthma refractory to approved therapies.

The majority of approved therapies carry a broad indication statement for the treatment of asthma with the recommended clinical use of the products further outlined in clinical treatment guidelines. However, the approved indication for omalizumab deviates from this standard. Omalizumab is indicated for the treatment of moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids. Recommended use of omalizumab in the current step-wise treatment approach in clinical practice is further delineated in the clinical treatment guidelines.

2.5 Availability of Proposed Active Ingredient in the United States

To date, mepolizumab has not been approved in the United States or anywhere else in the world.

[11] Moore et al “Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program” Am. J. of Respiratory and Cri Car Med; Vol 181.4 (2010):315-323.

2.6 Important Safety Issues With Consideration to Related Biologics

Mepolizumab is the first monoclonal antibody targeting IL-5 being evaluated for BLA approval so there are no related products for comparison. As an immunomodulatory monoclonal antibody targeting IL-5, evaluation of systemic and local injection site reactions, neoplasms, and opportunistic infections are of particular interest in this development program. In addition, an imbalance in cardiac Serious Adverse Events (SAEs) was seen in the Phase 2b dose-ranging study (Study 97) prompting the sponsor to include cardiovascular safety in its Adverse Events of Special Interest (AESI). Each of these AESIs is discussed further in Section 6.3.4 of this review.

2.7 Summary of Presubmission Regulatory Activity Related to Submission

Table 1: Summary of Key Presubmission Regulatory Activities

Date	Interaction	Division Comments:
January 15, 2014	Pre-BLA	- The adequacy of data supporting the 100 mg SC dose, including bridging information for the 100 mg SC to 75 mg IV dose will be a review issue. - Justification for the proposed restriction of mepolizumab to a subset of asthma patients will be expected. The Division recommends including any data from negative studies in a wider asthmatic population. - The BLA submission and proposed labeling will need to address the potential impact of mepolizumab on underlying parasitic disease. A PMR may be required.
May 4, 2012	EOP2	- The clinical program should define a patient population that can be clearly described in the product label and readily identified in the real-world. • Using inclusion criteria based on the ATS Severe Asthma workshop is reasonable; however, concerns were raised regarding the real-world applicability of the specific criteria used to define eosinophilic inflammation. • The clinical program will need to justify the restriction of mepolizumab to a subset of asthma patients. Information from other asthma populations will assist in the risk-benefit assessment and may be included in product labeling to assist clinicians in selecting appropriate patients. • The Division expressed concern regarding defining

Date	Interaction	Division Comments:
		a phenotype based on a single serum eosinophil measurement and noted that repeat measurements over time may be more reliable. - The clinical program should address the appropriate duration of therapy, i.e. when to discontinue treatment if a reduction in exacerbations has been achieved. - The definition of asthma exacerbation is reasonable. - The current clinical program will not demonstrate a comparative efficacy or safety benefit over corticosteroids.
April 21, 2009	Type B Advice meeting	- The Division agreed that recent published data suggests an asthma population that may benefit from treatment; however, the targeted patient population for the development program was unclear. The Division recommended evaluating mepolizumab in a range of asthma severity. - The range of proposed doses appears reasonable for the dose-ranging study. - The Division agrees with the evaluation of exacerbation data in addition to lung function data; however, the exacerbation definition should incorporate objective measures to account for variability in the exacerbation identification. - Proposed Phase 2b dose-ranging study may serve as a pivotal study if the studied population reflects the intended target population. - If the targeted population is defined in part by sputum eosinophil measurements, data to support and validate the sputum eosinophil measurement will be expected.
February 23, 2006	Advice meeting	- A clinical development program should include adequate and well-controlled trials in patients with less severe forms of asthma to address whether the product is safe and effective in this population.
February 24, 1997	IND safe to proceed	IND opened

3 Overview of the Clinical Program

The key studies from the applicant's BLA for mepolizumab discussed in this briefing package are outlined in Table 2. Key efficacy studies include Study 97, a pivotal dose-ranging and exacerbation efficacy study, Study 88, a second exacerbation study, and Study 75, a steroid-reduction study. Supplemental data are drawn from Study 06, an earlier, lung function study in less severe asthmatics that failed to demonstrate a treatment effect, and Study 92, a PK/PD, IV to SC bridging study. The safety database is composed of data from the three pivotal efficacy studies and supplemented by two, open-label extension studies providing longer-term safety data, Studies 61 and 66.

The targeted patient population for mepolizumab has continued to evolve over the course of its clinical development program. An early study, Study 06, in less severe asthma failed to demonstrate a beneficial impact on lung function[12] (see Sections 5.17 and 6.5.2 of this document). However, further evaluation in an investigator-sponsored study of mepolizumab in 61 patients with a history of 2 exacerbations requiring oral steroids and elevated sputum eosinophil counts > 3% on at least occasions in the previous 2 years provided initial evidence that mepolizumab decreased the number exacerbations in a more selective patient population[13].

Based on these data, the applicant conducted Study 97, a 52-week exacerbation and dose-ranging study in severe asthma further enriched for subjects with evidence of eosinophilic inflammation. In this study eosinophilic inflammation was defined using multiple biomarkers, including peripheral blood eosinophil counts, sputum eosinophilia, elevated Fractional exhaled Nitric Oxide (FENO), or loss of asthma control with reduction in corticosteroid dosing. Based on the positive results from Study 97, the applicant conducted a second exacerbation study, Study 88, and a steroid reduction study, Study 75, both of which further used criteria defining eosinophilic inflammation that was further refined (see Table 3 for an overview of the inclusion criteria for the pivotal efficacy studies).

Table 2: Key clinical studies

Study	Design	Duration	Population	N	Treatment Arms	Primary Efficacy Assessment	Study Sites (US subjects)
Pivotal Efficacy and Safety Studies							

[12] Flood-Page, Patrick, et al. "A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma." American journal of respiratory and critical care medicine 176.11 (2007): 1062-1071.
This GSK sponsored study, Study 06. is discussed in more detail in Section 5.17 and 6.52 of this review.
[13] Haldar, Pranabashis, et al. "Mepolizumab and exacerbations of refractory eosinophilic asthma." New England Journal of Medicine 360.10 (2009): 973-984.

Study	Design	Duration	Population	N	Treatment Arms	Primary Efficacy Assessment	Study Sites (US subjects)
MEA112997 (Study 97) *Nov 2009 to Dec 2011*	MC, R, DB, PC, PG,	52 weeks	severe asthma with eosinophilic inflammation*	153 152 156 155	Mepo 75 IV Mepo 250 IV Mepo 750 IV Placebo IV	Annualized rate asthma exacerbation	189 centers in 13 countries[1] *US: n = 78(13%)*
MEA115588 (Study 88) *Oct 2012 to Jan 2014*	MC, R, DB, DD, PC, PG,	32 weeks	severe asthma with eosinophilic inflammation*	194 191 191	Mepo 100 SC Mepo 75 IV Placebo	Annualized rate asthma exacerbation	119 centers in 16 countries[2] *US: n= 67 (12%)*
MEA115575 (Study 75) *Oct 2012 to Dec 2013*	MC, R, PC, PG,	24 weeks	severe asthma with eosinophilic inflammation*	69 66	Mepo 100 SC Placebo	Reduction in steroid dose while maintaining asthma control	38 centers in 10 countries[3] *US: n = 7 (5%)*
Long-term Safety Studies							
MEA115666 (Study 66) *Sept 2012 –*	OLE	~ 3.5 years *ongoing at time of submission*	Subjects from Study 97 12 month break	347	100 mg SC	Safety	65 centers in 13 countries[4] US: n = 30 (9%)
MEA115661 (Study 61) *May 2013 --*	OLE	52 weeks *ongoing at time of submission*	Subjects from Studies 88 & 75 No break in treatment	651	100 mg SC	Safety	139 centers in 19 countries[5] US: n = 66 (10%)
Supplemental Studies							
MEA114092 (Study 92) *Feb 2011 to Sept 2014*	R, OL, IV to SC bridging study	12 weeks	Asthmatics	21 15 23 11	Mepo 12.5SC Mepo 125 SC Mepo 250 SC Mepo 75 IV	PK/PD	11 centers in 4 countries[6] US: n = 5 (7%)

Study	Design	Duration	Population	N	Treatment Arms	Primary Efficacy Assessment	Study Sites (US subjects)
SB-240563/006 (Study 06) *Feb 1999 to Oct 1999*	MC, R, DB, PC, PG	12 weeks	≥ 18 – 55 year old asthmatics - FEV1 ≥ 50% and ≤ 80% - On ICS controller therapy - No exacerbation requirement - No eosinophil inflammation requirement	120 116 126	Mepo 250 IV Mepo 750 IV Placebo	peak expiratory flow	55 centers in 5 countries[7] US: n = 211 (58%)

* Additional enrichment criteria identified by the sponsor as indicative of airway eosinophilic inflammation. See Table 3 for the specific enrichment criteria used in each study.
[1] Argentina (4), Australia (5), Canada (5), Chile (4), France (5), Germany (9), Korea (2), Poland (5), Romania (5), Russian Federation (8), UK (5), Ukraine (7), United States (17)
[2] Argentina (7), Australia (3), Belgium (4), Canada (10), Chile (3), France (8), Germany (10), Italy (8), Japan (18), Republic of Korea (11), Mexico (1), Russian Federation (4), Spain (5), Ukraine (5), United Kingdom (5), and USA (18)
[3] Germany (8), France (5), Czech Republic (5), USA (5), United Kingdom (4), Australia (3), Canada (3), Netherlands (2), Poland (2), Mexico (1)
[4] United States (19), Japan (18), Germany (12), Canada (11), France (11), Korea (10), Italy (8), Argentina (7), United Kingdom (5), Czech Republic (5), Spain (5), Australia (4), Belgium (4), Russian Federation (4), Ukraine (4), Chile (3), Mexico (2), Netherlands (2), Poland (2)
[5] United States (11), Germany (8), Russian Federation (7), Australia (5), Romania (4), Ukraine (5), United Kingdom (5), Argentina (4), Canada (4), Chile (4), France (4), Korea (2), Poland (2)
[6] United States (1), Germany (4), Estonia (2), France (3)
[7] United States (30), France (10), Germany (9), Netherlands (2), UK (4)

MC = multi-center, R = randomized, PC = placebo-controlled, PG = parallel-group, OLE= open label extension, OL = open-label; PK = pharmacokinetic, PD = pharmacodynamic, yo= years old, mepo = mepolizumab, IV = intravenous, SC = subcutaneous

Table 3: Key inclusion criteria from pivotal efficacy studies: Studies 97, 88, 75

<table>
<tr><th></th><th>Study 97</th><th>Study 88</th><th>Study 75</th></tr>
<tr><td>Baseline asthma therapy</td><td colspan="2">High dose ICS + controlled therapy ± oral corticosteroids</td><td>High dose ICS + controller + oral corticosteroids</td></tr>
<tr><td>Exacerbation history</td><td colspan="2">≥ 2 exacerbations/year</td><td>No exacerbation history requirement</td></tr>
<tr><td>Eosinophilic airway inflammation criteria</td><td>• Serum eos ≥ 300 or
• Sputum eos > 3% or
• FENO ≥ 50 ppb or
• Loss of asthma control after 25% reduction in ICS/OCS</td><td>• Serum eos ≥ 150 at screening or
• Serum eos ≥ 300 in past 12 months</td><td>• Serum eos ≥ 150 at screening or
• Serum eos ≥ 300 in past 12 months</td></tr>
<tr><td colspan="4">ICS = inhaled corticosteroid, eos = eosinophil, FENO = Fractional exhaled Nitric Oxide, OCS = oral corticosteroids</td></tr>
</table>

4 Clinical Development Program – Study Design

4.1 Pivotal Efficacy and Safety Studies

4.1.1 Study MEA112997: Phase 2 Dose Finding Study (Study 97)

Title: A multicenter, randomized, double-blind, placebo-controlled, parallel group, dose ranging study to determine the effect of mepolizumab on exacerbation rates in subjects with severe uncontrolled refractory asthma

Study Centers: Eighty-one centers in 13 countries: Argentina (4), Australia (5), Canada (5), Chile (4), France (5), Germany (9), Korea (2), Poland (5), Romania (5), Russian Federation (8), UK (5), Ukraine (7), United States (17)

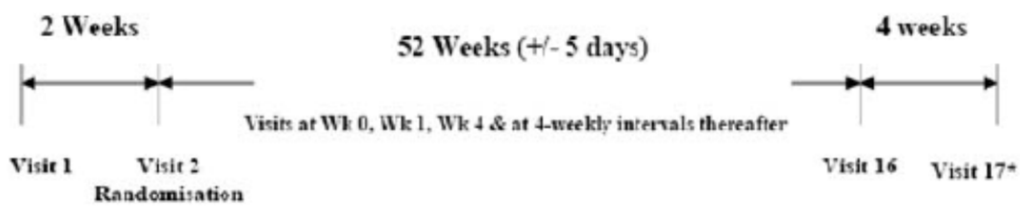
Study Dates: November 9, 2009 – December 5, 2011

<u>Study Design</u>
The study was a multi-center, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the effect of mepolizumab on exacerbation rates

in adult and adolescent subjects ≥ 12 years of age with asthma requiring treatment with high dose ICS for the prior 12 months (with or without corticosteroids) plus an additional controller medication (LABA, LTRA, or theophylline). Subjects were also required to meet at least one of several criteria the sponsor selected as biomarkers that may be indicative of eosinophilic inflammation.

Following an initial screening visit, subjects underwent a 2-week run-in period during which the subject's maintenance asthma medications remained unchanged. Subjects were randomized (stratified by maintenance oral corticosteroid use) to one of four treatments groups in a 1:1:1:1 fashion at the randomization visit (Visit 2). Treatment arms, given in addition to stable background therapy, included: mepolizumab 75 mg IV, 250 mg IV, 750 mg IV, or placebo. Treatment was administered every four weeks for 48 weeks providing for 52 weeks of treatment. Following a four-week safety follow-up period, subjects attended a follow-up visit at Visit 17 and returned to the clinic to provide a blood sample 24 weeks after the last dose of study medication for immunogenicity testing.

Figure 6: Study 97 Schematic



Source: Study 97 CSR Figure 1

The primary efficacy endpoint was the rate of exacerbations defined by the following criteria:

- Worsening of asthma which in the investigator's opinion requires use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits. For subjects on maintenance oral corticosteroids, an exacerbation requiring oral corticosteroids was defined as the use of oral/systemic corticosteroids at least double the existing dose for at least 3 days.

In attempt to standardize the clinical decision defining an exacerbation, the investigator was instructed to take into account changes from baseline in one or more of the following parameters recorded in the subject's e-Diary:

- A decrease in morning peak flow
- An increase in the use of rescue medication
- Increases in the frequency of nocturnal awakening due to asthma symptoms requiring rescue medication use
- An increase in overall asthma symptom score

<u>Study Population</u>

The inclusion/exclusion criteria for this study allowed for enrollment of subjects with severe refractory asthma ≥ 12 years of age with documented asthma requiring treatment with high dose ICS with or without maintenance oral corticosteroids in the prior 12 months plus an additional controller medication. Subjects had to have a history of ≥ 2 exacerbations requiring treatment with > 3 days of systemic corticosteroids and/or ER visit/hospitalization in the prior 12 months and were further required to meet criteria the sponsor had chosen to indicate evidence of eosinophilic airway inflammation.

Of note, there was no requirement that patients be symptomatic on background therapy as assessed by a daily asthma symptom assessment during the 2-week run-in period. The key inclusion, exclusion, and randomization criteria for the study are outlined below.

Key Inclusion Criteria

- Male or female non-smoking subjects ≥ 12 years of age with a minimum weight of 45 kg
- Evidence of asthma as documented by:
    - Airway reversibility (FEV1 ≥ 12% and 200 ml) at Visit 1 or Visit 2 or documented in the previous 12 months OR
    - Airway hyperresponsiveness (PC_{20} of < 8 mg/ml or PD_{20} < 7.8 μmol methacholine/histamine) documented in past 12 months OR
    - Airflow variability in clinic FEV1 ≥ 20% between two consecutive clinic visit documented in the 12 months prior to Visit 1 (FEV_1 recorded during an exacerbation will not be valid) OR
    - Airflow variability as indicated by > 20% diurnal variability in peak flow observed on ≥ 3 days during run-in
- Clinical features of severe refractory asthma similar to those outlined in the ATS Workshop on Refractory Asthma[14] for ≥ 12 months prior to Visit 1 and mandated by meeting the following inclusion criteria
    - Treatment with high dose ICS (with or without oral corticosteroids) in the 12 months prior to Visit 1
    - Treatment with an additional controller medication (LABA, LTRA, or theophylline) in the 12 months prior to Visit 1
    - Persistent airflow obstruction with pre-bronchodilator FEV_1 < 80% at Visit 1 or Visit 2 or peak flow diurnal variability of > 20% on 3 or more days during run-in
    - History of ≥ 2 exacerbations requiring treatment with oral corticosteroids in the prior 12 months despite use of high-dose ICS and additional controller medications. For patients receiving maintenance OCS with high-dose ICS plus controller, the OCS treatment for exacerbation must be a two-fold or greater increase in dose of OCS.

[14] "Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions." American Thoracic Society. Am J Respir Crit Care Med 2000: 162(6): 2341-2351.

- Airway inflammation likely to be eosinophilic in nature
    - Elevated peripheral blood eosinophil count ≥ 300 cells/µL OR
    - Sputum eosinophil 3% OR
    - Fractional exhaled Nitric Oxide ≥ 50 ppb (performed at Visit 1 or Visit 2 pre randomization) OR
    - Prompt deterioration of asthma control following a ≤ 25% reduction in regular maintenance dose of inhaled or oral corticosteroid dose in previous 12 months

Key Exclusion criteria

- Current smokers or subjects with smoking history ≥ 10 pack years
- Clinically important lung conditions other than asthma
- Subjects who have received Xolair or any other biological for the treatment of inflammatory disease within 130 days of Visit 1
- Regular use of oral or systemic corticosteroids for diseases other than asthma within the past 12 months
- Subjects with parasitic infection within 6 months of Visit 1
- Subjects with clinically significant cardiovascular, endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, hematologic, or any other system abnormalities that are uncontrolled with standard treatment

Key Randomization Criteria Following Run-in

- No changes in asthma medication (excluding rescue salbutamol/albuterol MDI provided at Visit 1) during run-in
- No respiratory tract infection that led to a change in asthma management and no exacerbations during run-in (defined as worsening asthma requiring systemic corticosteroids and/or ER visit or hospitalization)

<u>Investigational Treatment</u>

- Mepolizumab 75 mg IV
- Mepolizumab 250 mg IV
- Mepolizumab 750 mg IV
- Matching IV placebo

<u>Withdrawal Criteria</u>

- Investigator/subject discretion
- Meeting specific ECG or LFT withdrawal criteria

<u>Study Assessments</u>

The timing of the key efficacy and safety assessments evaluated in this study are summarized in Table 4.

Table 4: Key efficacy and safety assessments: Study 97

	Screen/ run-in	Random -ization	Treatment				Early with-drawal	End of Therapy	F/U
Visit	**1**	**2**	**3**	**4**	**5-14**	**15**		**16**	**17**
Week	**-2 ± 2d**	**0**	**1±2 d**	**4±5 d**	**8-44**	**48± 5d**		**52±5d**	**56±5 d**
Efficacy									
Exacerbation review		x	x	x	x	x	x	x	
Spirometry	x	x	x	x	x	x	x	x	
ACQ		x		x	x	x	x	x	
eDiary data review (PEF, symptoms)		x	x	x	x	x	x	x	
Safety									
Concomitant meds	x	x	x	x	x	x	x	x	
PE	x						x	x	
VS	x	x	x	x	x	x	x	x	
12-lead ECG	x				x		x		x
AE		x	x	x	x	x	x	x	x
SAE	x	x	x	x	x	x	x	x	x
Laboratory									
Hematology	x	x		x	x	x	x	x	x
Chemistry	x	x		x	x	x	x	x	
UA	x			x	x	x	x	x	
Blood eosinophils	x	x		x	x	x	x	x	x
Immunogenicity		x			x	x	x		x
Source: Study 97 Protocol Table 3									

<u>Efficacy Endpoints:</u>

Primary Efficacy Endpoint

- Frequency of exacerbations defined by worsening of asthma which in the investigators opinion required oral/systemic corticosteroids[15] and/or hospitalization and/or ED visit

[15] For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.

Investigators were instructed to take the following into account when making the exacerbation assessment:

- Decrease in morning peak flow
- Increase in the use of rescue medication
- Increase in the frequency of nocturnal awakening due to asthma symptoms requiring rescue medication use

Secondary Efficacy Endpoints

- Time to first clinically significant exacerbation
- Frequency of exacerbations requiring hospitalization (including intubation and admittance to an intensive care unit) or ED visit
- Frequency of Investigator-defined exacerbations
- Time to first Investigator-defined exacerbation
- Mean change from baseline in clinic pre-bronchodilator FEV1 over the 52-week treatment period
- Mean change from baseline in clinic post-bronchodilator FEV1 over the 52-week treatment period
- Mean change from baseline in Asthma Control Questionnaire (ACQ) score

Pre-specified Statistical Methods

Exacerbation rates were analyzed using a generalized linear model with negative binomial distribution having independent factors treatment, OCS usage at baseline, region, number of exacerbations in year prior to study, and baseline disease severity (% predicted FEV1). The planned offset was logarithm of time followed for exacerbations. Type I error across doses for the rate of exacerbations, the primary endpoint was controlled by first testing for a linear trend across doses, including placebo and following with tests of each dose versus placebo only if the overall trend was significant. Control of type I error across doses in the secondary endpoints was achieved with a truncated Hochberg procedure. Endpoints were tested in the hierarchical order listed below.

1. Rate of exacerbations
2. FEV1 pre-bronchodilator at week 52
3. AQLQ at week 52
4. Rate of exacerbations requiring hospitalizations or emergency department visits
5. ACQ-6 at week 52

4.1.2 Study MEA115588: Phase 3 Exacerbation Study (Study 88)

Title:	A randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multi-center study of the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe uncontrolled refractory asthma
Study Centers:	A total of 119 centers in 16 countries randomized and treated subjects: Argentina (7), Australia (3), Belgium (4), Canada (10), Chile (3), France (8), Germany (10), Italy (8), Japan (18), Republic of Korea (11), Mexico (1), Russian Federation (4), Spain (5), Ukraine (5), United Kingdom (5), and USA (18).

Study Dates: October 2, 2012- January 18, 2014

Study 88 was a randomized, double-blind, double-dummy, placebo-controlled, parallel-group study in a severe asthma population enriched for markers the sponsor has identified as indicative of eosinophilic inflammation. While similarly designed to Study 97, there were several key differences in the study design which are outlined below.

Similar to Study 97, the targeted study population in Study 88 included adults and adolescents 12 years of age and older with severe asthma defined by use of high dose ICS therapy plus an additional controller therapy who experienced ≥ 2 exacerbations in the prior year requiring treatment with systemic corticosteroids for ≥ 3 days and/or ER visit/hospitalization. However, in contrast to Study 97, Study 88 relied on different criteria to enrich for evidence of eosinophilic inflammation. In this case, the sponsor enrolled subjects with a peripheral blood value ≥ 300 cells/µLin the prior 12 months or an elevated peripheral blood eosinophil count ≥ 150 cells/µL at Visit 1 (screening) related to asthma.

The same primary endpoint used in Study 97, the annual rate of exacerbations, was used in this study; except the study had a shorter treatment period of 32 weeks compared to the 52 weeks evaluated in Study 97. The study also evaluated both a 75 mg IV and 100 mg SC mepolizumab doses in addition to matching placebo.

Pre-specified Statistical Methods

Exacerbation rates were analyzed using a generalized linear model with negative binomial distribution having independent factors treatment, OCS usage at baseline, region, number of exacerbations in year prior to study, and baseline disease severity (% predicted FEV1). The planned offset was logarithm of time followed for exacerbations.

Type I error over multiple doses and endpoints was controlled using a truncated Hochberg procedure conducted at the one-sided 0.025 level of significance. Significance for an endpoint was declared if both doses compared to placebo were significant at the unadjusted 0.025 level or if at least one dose compared to placebo was significant at the unadjusted 0.0125 level. If both of the dose comparisons to placebo for an endpoint were significant at the one-sided unadjusted 0.025 level, then the next endpoint in the hierarchy provided below was tested. The gamma parameter for the Hochberg procedure was 1:

1. Exacerbation rate
2. Severe exacerbation rate
3. Hospitalization rate
4. ∆Trough FEV1 W32
5. ∆SGRQ at W32

4.1.3 Study MEA115575: Steroid Reduction Study (Study 75)

Title:	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study of Mepolizumab Adjunctive Therapy to Reduce Steroid Use in Subjects with Severe Refractory Asthma
Study Centers:	38 centers in 10 countries: Germany (8), France (5), Czech Republic (5), USA (5), United Kingdom (4), Australia (3), Canada (3), Netherlands (2), Poland (2), Mexico (1)
Study Dates:	October 29, 2012 – December 12, 2013

Study Design:
The study was a multicenter, randomized (stratified by previous oral corticosteroid use of less or more than 5 years), placebo-controlled, double-blind, parallel-group designed study with a 24-week treatment period. With the exception of oral corticosteroid dose titration, all subjects remained on their existing maintenance asthma therapy throughout the duration of the study. The study included 4 study periods which are outlined below:

1. Oral corticosteroid optimization phase used to titrate a subject to the lowest oral corticosteroid dose that maintained control of their symptoms (3- 10 weeks duration): A recommended dose titration schedule was provided, but not required, for use by investigators (Table 5).
2. Induction phase (4 weeks duration): Subjects received their first dose of blinded investigational treatment and remained on their optimized oral corticosteroid dose.
3. Oral corticosteroid reduction phase (16 weeks duration): 5 doses of investigational product were administered during this phase. Investigators were provided with recommended OCS dose titration schedule and assessed subjects for dose reduction every 4 weeks (Table 6).
4. Maintenance (4 weeks duration): No further oral corticosteroid dose adjustments were made during this phase. Subjects who met eligibility criteria were offered enrollment in a 12-month open-label extension study (Study 61).

Table 5: Optimization phase OCS dose titration schedule

Sequential Time Course	Prednisone/prednisolone Optimisation Phase								
	Oral Corticosteroid Dose (mg/day)								
Visit 2 starting dose	35	30	25	20	15	12.5	10.0	7.5	5.0
1st dose reduction (Visit 2)	30.0	25.0	20.0	15.0	12.5	10.0	7.5	5.0	5.0
+ 1 Week	25.0	20.0	15.0	12.5	10.0	7.5	5.0		
+ 1 Week	20.0	15.0	12.5	10.0	7.5	5.0			
+ 1 Week	15.0	12.5	10.0	7.5	5.0				
+ 1 Week	12.5	10.0	7.5	5.0					
+ 1 Week	10.0	7.5	5.0						
+ 1 Week	7.5	5.0							
+1 Week	5.0								

Source: Study 75 Protocol Table 1

A suggested OCS tapering schedule (Table 6) was provided to study sites for OCS reduction unless one or more of the following occurred:

- Mean AM peak PEF < 80% of the baseline stability limit
- Mean asthma-related night time awakenings > 50% increase over the baseline period (per night), > 150% of the baseline mean
- Rescue medication use requiring ≥ 4 puffs/day above the mean baseline value for any 2 consecutive days in the prior week, or ≥ 12 puffs of any one day in the prior week
- Change in ACQ5 ≥ 0.5 from the prior months OCS dose assessment
- Symptoms of adrenal insufficiency

Table 6: Reduction phase OCS titration schedule: Study 75

Sequential Time Course	Prednisone/Prednisolone Reduction Phase								
	Oral Corticosteroid Dose (mg/day)								
Optimized OCS dose	35	30	25	20	15	12.5	10.0	7.5	5.0
1st dose reduction	25.0	20.0	15.0	10.0	10.0	10.0	5.0	5.0	2.5
+ 4 Weeks	15.0	10.0	10.0	5.0	5.0	5.0	2.5	2.5	1.25*
+ 4 Weeks	10.0	5.0	5.0	2.5	2.5	2.5	1.25*	1.25*	0
+ 4 Weeks	5.0	2.5	2.5	1.25*	1.25*	1.25*	0	0	0
+ 4 Weeks	2.5	2.5	2.5	0	0	0	0	0	0

1. *Subject taking 1.25mg/day should take this as 2.5mg administered every other day

Source: Study 75 Protocol Table 2

<u>Study Population</u>

The inclusion/exclusion criteria allowed for enrollment of subjects ≥ 12 years of age with asthma with a documented requirement for regular treatment with maintenance systemic corticosteroids (5 to 35 mg/day prednisone or equivalent) and high-dose-ICS in the 6 months prior to screening. Subjects also had to be receiving current treatment with an additional controller medication for at least 3 months or have documentation of failure with an additional controller medication for at least 3 consecutive months during the prior 12 months and demonstrate evidence of asthma and persistent airflow obstruction. As with Studies 97 and 88, the sponsor further enriched the population with markers it believes are indicative of airway eosinophilic inflammation. The eosinophilic inflammation enrichment criteria were the same as those outlined in Study 88 and required subjects to have a history of an elevated peripheral blood eosinophil count ≥ 300 cells/μL related to asthma within the previous 12 months or a peripheral blood eosinophil count ≥ 150 cells/μL at screening Visit 1. In this study, subjects had to achieve a stable dose of OCS, defined as 2 weeks on the same OCS dose between 5 and 35 mg/day of OCS, during the optimization period. Subjects were not required to have an exacerbation history.

Investigational Treatment

- Mepolizumab 100 mg SC every 4 weeks
- Matching placebo

Efficacy Endpoints

Primary

- Percent reduction of OCS dose during weeks 20-24 compared to baseline dose, while maintaining asthma control

Secondary (with no correction for multiple endpoints)

- Proportion of subjects who achieve a 50% reduction or greater in their daily OCS dose, compared to baseline dose, during weeks 20-24 while maintaining asthma control
- The proportion of subjects who achieve a reduction of their daily OCS dose to less than or equal 5 mg during weeks 20-24, while maintaining asthma control
- The proportion of subjects who achieve a total reduction of OCS dose during weeks 20-24, while maintaining asthma control
- Median percentage reduction from baseline in daily OCS dose during weeks 20-24 while maintaining asthma control

Notably, the annualized rate of exacerbations, FEV1, SGRQ and ACQ were evaluated as “other endpoints” in this study.

Pre-Specified Statistical Methods

Comparison of mepolizumab to placebo for percent reduction of daily prednisone dose while maintaining asthma control was analyzed using a proportional odds model with the following categories of percent reduction: 0%, >0% to <50%, 50% to <75%, 75% to 90%, and 90% to 100%. The model included independent variables treatment, number of years on OCS (< 5 years, ≥ 5 years), region, and baseline OCS dose.

4.2 Long-term Safety Studies

4.2.1 MEA115661 Open Label Extension for subjects enrolled in Studies 88 and 75 (Study 61)

Title:	A multi-center, open-label, long-term safety study of mepolizumab in asthmatic subjects who participated in the MEA115588 or MEA115575 studies
Study Centers:	139 centers in 19 countries: United States (19), Japan (18), Germany (12), Canada (11), France (11), Korea (10), Italy (8), Argentina (7), United Kingdom (5), Czech Republic (5), Spain (5), Australia (4), Belgium (4), Russian Federation (4), Ukraine (4), Chile (3), Mexico (2), Netherlands (2), Poland (2)
Study Dates:	May 21, 2013 – on-going (interim report data cutoff date: Feb 28, 2014)

This study was a multicenter, open-label, long-term safety study of mepolizumab 100 mg SC every 4 weeks on continued background standard of care in subjects who completed Study 88 or study 75. The study was 52 weeks in duration and subjects with a history of life-threatening disease and a history of improved asthma disease control while receiving mepolizumab are eligible for extended treatment in Study 201312, an open-label access study in patients from Study 61 with a history of life-threatening/seriously debilitating asthma who have demonstrated a positive mepolizumab treatment response. Data from Study 201312 were not available at the time of BLA submission and only limited safety data from this study were provided in the 120-day safety update.

4.2.2. MEA115666 Open Label Extension for subjects enrolled in Study 97 (Study 66)

Title:	A multi-center, open-label, long-term safety study of mepolizumab in asthmatic subjects who participated in the MEA112997
Study Centers:	65 centers in 13 countries: United States (11), Germany (8), Russian Federation (7), Australia (5), Romania (4), Ukraine (5), United Kingdom (5), Argentina (4), Canada (4), Chile (4), France (4), Korea (2), Poland (2)
Study Dates:	September 28, 2012 – on-going (interim report data cutoff date: Feb 28, 2014)

This study was a multicenter, open-label, long-term safety study of mepolizumab 100 mg SC every 4 weeks on continued background standard of care in subjects who completed Study 97. All enrolled subjects had a gap of at least 12 months from the last dose of double-blind study medication in Study 97 to enrollment in Study 66. Mepolizumab was dosed every 4 weeks until either: 1) the risk/benefit profile is no longer positive in the opinion of the investigator, 2) subject's physician withdraws the subject, 3) the subject withdraws consent, 4) sponsor discontinues development, 5) the sponsor discontinues the study in the relevant country, or 6) mepolizumab becomes commercially available in the relevant participating country.

5 Review of Efficacy

Efficacy Summary

The key efficacy studies in the mepolizumab clinical development program include a pivotal, 52-week, dose-ranging and exacerbation study (Study 97), a second, 32-week, exacerbation study (Study 88), and a steroid-reduction study (Study 75).

Studies 97 and 88 enrolled subjects with severe asthma on background ICS + controller therapy with a history of exacerbations and were further enriched with biomarkers the sponsor has identified as indicative of eosinophilic inflammation. Study 97 used the broadest criteria to identify these patients and included patients with elevated peripheral blood or sputum eosinophils, elevated FENO, or loss of control with reduction in steroid dosing. This study evaluated the annualized rate of exacerbations for three IV doses of mepolizumab against placebo: 75 mg IV, 250 mg IV, and 750 mg IV.

The sponsor subsequently included specific peripheral blood eosinophil cutoffs of ≥ 150 cells/µl at screening or history of counts ≥ 300 cells/µL into Study 88. Study 88 evaluated the annualized rate of exacerbations for mepolizumab 75 mg IV treatment and 100 mg SC against placebo. Study 75, an oral corticosteroid reduction study, used the same eosinophilic inflammation enrichment strategy and evaluated the effect of mepolizumab 100 mg SC against placebo on oral corticosteroid steroid dose reduction without loss of asthma control. Of note, this study did not require an exacerbation history, which is reasonable as subjects were maintained on chronic corticosteroids prior to enrolment.

The positive treatment effect with a lack of a dose-response seen in Study 97 along with the similar treatment response between the 75 mg IV and 100 mg SC treatment arms in Study 88 and data from the PK/PD Study 92 provides support for the 100 mg SC mepolizumab dose and route proposed for marketing.

Efficacy support for mepolizumab is provided by the two exacerbation studies, each of which demonstrated a statistically significant reduction in exacerbations for all of the evaluated mepolizumab doses. Additional support for the 100 mg SC dose is provided by Study 75 which demonstrated a statistically significant reduction in oral corticosteroid dose without loss of asthma control for subjects treated with 100 mg SC compared to placebo.

In addition to the efficacy data from the pre-specified analyses of the total enrolled population, the Agency and sponsor conducted multiple exploratory analyses to gain a better understanding of the treatment modification effect by peripheral blood eosinophil counts. Such analyses were discussed with the sponsor at the end-of-phase 2 meeting, which included a discussion of selecting blood eosinophils as a likely predictive biomarker. Statistical methods for this purpose were discussed internally prior to marketing application submission. Overall, the data suggest a strong trend towards an improved treatment response with higher levels of peripheral blood eosinophil counts obtained in close proximity to treatment initiation. These exploratory data should be considered within the context of the inherent variability that is observed in peripheral blood eosinophil measurements over time due to unknown intrinsic factors within an individual and the imprecision in measurements.

As noted in the executive summary, the Agency is requesting a panel discussion of the available efficacy data from this development program with a specific consideration of how these data can be used to inform the appropriate use of the product in clinical practice. In essence, the Agency is asking the panel to discuss the predictive value of a single peripheral blood eosinophil count and how much weight the prescribing clinician can place on use of this biomarker, either alone or in combination with other clinical considerations.

The adequacy of the data in African Americans is also of interest given the increased morbidity and mortality that is seen in this population. The panel is further asked to discuss the adequacy of the data from the adolescent population in this program. As noted in the executive summary of this clinical briefing document, approval of mepolizumab would trigger PREA. Should the panel feel that the targeted patient population for this biologic is relevant to the pediatric population and that additional study is needed, PREA grants the Agency regulatory authority to require additional pediatric studies.

5.1 Indication

The current proposed indication for mepolizumab is for the add-on maintenance treatment of patients ages 12 years of age and older with severe eosinophilic asthma identified by blood eosinophils greater than or equal to 150 cells/μL at initiation of treatment or blood eosinophils greater than or equal to 300 cells/μL in the past 12 months. The indication statement further stipulates that mepolizumab has been shown to reduce exacerbations of asthma in patients with an exacerbation history.

5.1.1 Methods

This review focuses on the efficacy results from three pivotal efficacy and safety studies: Study 97, Study 88, and Study 75. Additional efficacy data from Study 06 are reviewed in Section 5.1.7 to provide contextual information regarding use of the product in a milder asthmatic population. Details of the study designs for each of the pivotal studies can be found in Section 4, the study design for Study 06 is summarized in Section 5.1.7.

5.1.2 Demographics

Overall the age, gender, race and asthma severity were similar across treatment groups within each pivotal study. Subjects were more commonly female (59%) and White (85%) with a mean age of 49 years. The mean duration of asthma was 19 years, over 90% were taking ICS/LABAs, and 38% of subjects were taking maintenance OCS. Despite maximum standard of care therapy, over half the subjects had experienced ≥ 3 exacerbations in the prior year. The majority of subjects had never smoked (74%).

Overall, an underrepresentation of subjects of African Heritage and adolescents age 12 to 17 years old are evident in this development program. The enrollment of these subgroups relative to the US population and the efficacy data for these subgroups is discussed in Section 5.1.6.

Table 7: Baseline demographics and disease characteristics: Study 97

		Mepolizumab		
	Placebo IV N = 155	**75 IV N = 153**	**250 IV N = 152**	**750 IV N = 156**
Age (years)				
Mean (range)	46 (20-68)	50 (23-69)	49 (15-74)	49 (19-69)
Sex (n, %)				
Female	97(63)	104 (68)	93(61)	93 (60)
Male	58 (37)	49 (32)	59 (39)	63 (40)
Race (n,%)				
White	140 (90)	139 (91)	135 (89)	140 (90)
Asian	8 (5)	9 (6)	7 (5)	10 (6)
African Heritage	6 (4)	5 (3)	8 (5)	5 (3)
American Indian or Al. Native	0	0	0	1 (<1)
Native Hawaiian or	1(<1)	0	0	0

		Mepolizumab		
	Placebo IV N = 155	**75 IV N = 153**	**250 IV N = 152**	**750 IV N = 156**
Pacific Islander				
Other	0	0	2(1)	0
Ethnicity (n, %)				
Hispanic or Latino	16 (10)	15 (10)	14 (9)	16 (10)
Not Hispanic or Latino	139 (90)	138 (90)	138 (91)	140 (90)
Asthma Duration (n, %)				
≥ 1 to < 10 years	51	43	38	55
≥ 10 years to < 20 years	40	44	42	36
≥ 20 years	43	66	72	65
Post-bronchodilator % Predicated FEV1				
Mean	71.4	70.0	70.3	70.4
FEV1/FVC ratio (%)				
Mean	0.66	0.67	0.66	0.68
% reversibility (%)				
Mean	26.8	22.6	25.6	23.9
Smoking Status n (%)				
Never smoked	121 (78)	122 (80)	121(80)	119 (76)
Former smoker	34 (22)	31 (20)	31 (20)	37 (24)
Baseline Eosinophil Count, cells/µL (SD)				
Baseline	418 (372)	367 (350)	390 (435)	361 (310)
Source: Study 97 CSR Table 8, 5.15, 5.18, FDA Statistical Reviewer Analysis				

Table 8: Baseline demographics and disease characteristics: Study 88

		Mepolizumab	
	Placebo N = 191	**100 SC N = 194**	**75 IV N = 191**
Age (years)			
Mean (range)	49(12-76)	51(12-81)	50(13-82)
Sex (n, %)			
Female	107(56)	116(60)	106(55)
Male	84 (44)	78 (40)	85 (45)
Race (n,%)			
White	148 (77)	152 (78)	151 (79)
Asian	38 (20)	34 (18)	33 (17)
African Heritage	3 (2)	7 (4)	6 (3)
Amer. Indian or Alaska Native	0	1 (<1)	0
Native Hawaiian or	0	0	0

		Mepolizumab	
	Placebo N = 191	**100 SC N = 194**	**75 IV N = 191**
Pacific Islander			
Other	2	0	1
Ethnicity (n, %)			
Hispanic or Latino	15 (8)	18 (9)	18 (9)
Not Hispanic or Latino	176 (92)	176 (91)	173 (91)
Asthma Duration (n, %)			
≥ 1 to < 10 years	47(25)	40(21)	52(27)
≥ 10 years to < 20 years	71(37)	61(31)	58(30)
≥ 20 years	73(38)	93(48)	81(42)
% predicated post-bronchodilator FEV1			
mean	72.3	69.9	70.5
FEV1/FVC ratio (%)			
mean	0.67	0.66	0.67
% reversibility FEV1 (%)			
mean	27.2	28.7	27.2
Smoking History (n, %)			
Never smoked	134 (70)	144 (74)	139 (73)
Former smoker	57 (30)	50 (26)	52 (27)
Eosinophil Inclusion Criteria, n (%)			
≥ 300 cells/μL	121 (63)	146 (75)	130 (68)
≥ 150 cells/μL	167 (87)	155 (80)	155 (81)
Exacerbations in prior year			
mean	3.6	3.8	3.5
Baseline Eosinophil Count, cells/μL (SD)			
mean	460 (450)	451 (437)	417 (399)

[+] one subject in Korea was incorrectly noted as being Hispanic/Latino
Source: Study 88 CSR Tables 6, 7, 8, 9, FDA Statistical Reviewer Analysis

Table 9: Baseline demographics and disease characteristics: Study 75

	Placebo N = 66	**Mepo 100 SC N = 69**
Age (years)		
Mean (range)	50 (28-70)	50 (16-74)
Sex (n, %)		
Female	30 (45)	44 (64)
Male	36 (55)	25 (36)
Race (n,%)		

	Placebo N = 66	**Mepo 100 SC N = 69**
White	61 (92)	67 (97)
Asian	2 (3)	1 (1)
African Heritage	0	0
American Indian or Alaska Native	1 (2)	0
Native Hawaiian or Pacific Islander	1 (2)	0
Other	1 (2)	1 (1)
Ethnicity (n, %)		
Hispanic or Latino	3 (5)	2 (3)
Not Hispanic or Latino	63 (95)	67 (97)
Asthma Duration (n, %)		
≥ 1 to < 10 years	19 (29)	23 (33)
≥ 10 years to < 20 years	20 (30)	17 (25)
≥ 20 years	27 (41)	29 (42)
Post-bronchodilator % predicated FEV1		
mean	67.6	71.8
FEV1/FVC ratio (%)		
mean	0.64	0.67
% reversibility FEV1 (%)		
mean	23.7	24.9
Smoking History, (n, %)		
Never smoked	41 (62)	41 (59)
Former smoker	25 (38)	28 (41)
Duration of OCS use at baseline, n (%)		
<5 years	35 (53)	35 (51)
≥ 5 years	31 (47)	34 (49)
Daily OCS dose, (mg) at baseline		
Mean (range)	13 (5-35)	12 (5-35)
Eosinophil Inclusion Criteria, n (%)		
≥ 300 cells/μL within 12 months	42 (64)	50 (72)
≥ 150 cells/μL at Baseline	60 (91)	61 (88)
Exacerbations in Prior Year		
Mean	2.9	3.3
Baseline Eosinophil Count, cells/μL (SD)		
Mean	408 (375)	344 (296)
Source: Study 75 CSR Table 9, 10, 11, 12, 13, 5.21, FDA Statistical Reviewer Analysis		

All subjects enrolled in the severe asthma studies were on concomitant asthma therapy prior to enrollment. As outlined in the protocols, all subjects were taking background high dose ICS in addition to other asthma controller therapies. In keeping with clinical practice, the majority were taking an ICS/LABA, with many taking an additional controller medication (Table 10). Per the protocols, the background therapy was maintained throughout the run-in and treatment periods.

Table 10: Respiratory medications prior to run-in: Studies 97, 88, 75

		Mepolizumab			
	Placebo	**100 SC**	**75 IV**	**250 IV**	**750 IV**
Study 97					
Asthma Meds prior to run-in					
ICS + LABA alone	86 (55)	--	92 (60)	80 (53)	94 (60)
ICS + LABA + additional controller	63 (41)	--	50 (33)	61 (40)	57 (37)
ICS + non-LABA controller	1 (<1)	--	3 (2)	2 (1)	0
Study 88					
Asthma Meds Prior to run-in					
ICS + LABA alone	76 (40)	72 (37)	80 (42)	--	--
ICS + LABA + additional controller	110 (58)	119 (61)	102 (53)	--	--
ICS + non-LABA controller	1 (<1)	0	3 (2)	--	--
Study 75					
Asthma Meds Prior to run-in					
ICS + LABA alone	24 (36)	29(42)	--	--	--
ICS + LABA + additional controller	41 (62)	40 (58)	--	--	--
ICS + non-LABA controller	1(2)	0	--	--	--
Source: January 20, 2015 Response to Clinical Information Request Tables 1,2,3					

5.1.3 Subject Disposition

No imbalances in the rates of treatment withdrawal across treatment arms in each of the pivotal efficacy and safety studies are seen.

		Mepolizumab			
	Placebo	**100 SC**	**75 IV**	**250 IV**	**750 IV**
Study 97 n, (%)					
Randomized	155	--	153	152	156
Completed	127 (82)	--	129 (84)	131 (86)	133 (85)
Withdrawn	28 (18)	--	24 (16)	21 (14)	23 (15)
Adverse event[1]	6 (4)	--	5 (3)	8 (5)	9 (6)
Adverse event[2]	5 (3)	--	4 (3)	7 (5)	8 (5)
Lab abnormality	1 (<1)	--	1 (<1)	1 (<1)	1 (<1)
Lack of efficacy	8 (5)	--	6 (4)	4 (3)	4 (3)
Protocol deviation	1 (<1)	--	1 (<1)	0 (0)	0 (0)
Lost to follow up	1 (<1)	--	1 (<1)	4 (3)	0 (0)
Investigator discretion	1 (<1)	--	3 (2)	3 (2)	3 (2)

Withdrew consent	11 (7)	--	8 (5)	2 (1)	7 (4)
Study 88					
Randomized	191	194	191	--	--
Completed	179 (94)	185 (95)	175 (92)	--	--
Withdrawn	12 (6)	9 (5)	16 (8)	--	--
Subject discretion	5 (3)	4 (2)	9 (5)	--	--
Adverse event	4 (2)	1 (<1)	0 (0)	--	--
Lack of efficacy	1 (<1)	2 (1)	1 (<1)	--	--
Lost to follow up	0 (0)	2 (1)	2 (1)	--	--
Protocol deviation	0 (0)	0 (0)	3 (2)	--	--
Physician discretion	2 (1)	0 (0)	1 (<1)	--	--
Study 75					
Randomized	66	--	69	--	--
Completed	62 (94)	--	66 (96)	--	--
Withdrawn	4 (6)	--	3 (4)	--	--
Adverse Event	3 (5)	--	3 (4)	--	--
Withdrew consent	1 (2)	--	0	--	--

[1] adverse event leading to permanent discontinuation of investigational product or withdrawal from study
[2] subjects with "adverse event" as primary reason for withdrawal
Source: FDA Statistical Reviewer Analysis

Treatment Compliance

All IV and SC doses were administered within the study centers; therefore subject compliance with treatment is not in question. The table below summarizes the mean and median number of treatments administered for each treatment group within each study. No imbalances across treatment groups are noted.

Table 11: Number of treatments administered

		Mepolizumab			
	Placebo	**100 SC**	**75 IV**	**250 IV**	**750 IV**
Study 97					
Mean	11.6	--	11.8	12.0	11.8
Median	13	--	13	13	13
Study 88					
Mean	7.7	7.7	7.6	--	--
Median	8	8	8	--	--
Study 75					
Mean	5.9	5.8	--	--	--
Median	6	6	--	--	--

Source: Study 97 CSR Table 9, Study 88 CSR Table 10, Study 75 CSR Table 15

5.1.4 Analysis of Primary Endpoint(s)

5.1.4.1 Exacerbations: Studies 97, 88, 75[16]

The annualized rate of exacerbations was evaluated as the primary efficacy endpoint in Studies 97 and 88 and evaluated as an “other endpoint” in Study 75. This endpoint was not adjustment for multiplicity in Study 75 therefore results are nominally significant only.

Both Studies 97 and 88 demonstrated a statistically significant reduction in exacerbations with similar effect sizes demonstrated in each study. A numeric reduction in exacerbations is also seen in mepolizumab treated subjects compared to placebo in Study 75 (Table 12).

No dose response is evident from the data in Study 97 and similar effect sizes are seen between IV and SC treatment arms in Study 88. Notably, Study 88 was the only pivotal exacerbation study to evaluate the direct effect of the subcutaneous dosing on the exacerbation rate. The effect size between the two routes of administration in Study 88, along with data from the OCS withdrawal study (Study 75) and the results of the PK/PD study (Study 92), provide support for the efficacy of the chosen dose for marketing.

Table 12: The annual rate of exacerbations for Studies 97, 88, 75

		Mepolizumab			
	Placebo	**100 SC**	**75 IV**	**250 IV**	**750 IV**
Study 97					
N	155	--	153	152	156
Exacerbation/year	2.40	--	1.24	1.46	1.15
Δ placebo	--	--	-1.16	-0.94	-1.24
p-value	--	--	<0.0001	0.0006	<0.0001
Study 88					
N	191	194	191	--	--
Exacerbation/year	1.74	0.83	0.93	--	--
Δ placebo	--	-0.92	-0.81	--	--
p-value	--	<0.0001	<0.0001	--	--
Study 75					
N	66	69	--	--	--
Exacerbation/year	2.12	1.44	--	--	--

Source: FDA Statistical Reviewer Analysis and Modifications of Study 75 CSR Table 28

[16] exacerbations were not evaluated as the primary endpoint in Study 75 but as an “other endpoint”

Exploratory analyses of the exacerbation data by eosinophil count

As noted above, the sponsor's development program demonstrates a consistent, statistically significant treatment effect on exacerbations in a population of severe asthmatics with a history of exacerbations further enriched for biomarkers deemed to be indicative of eosinophilic inflammation.

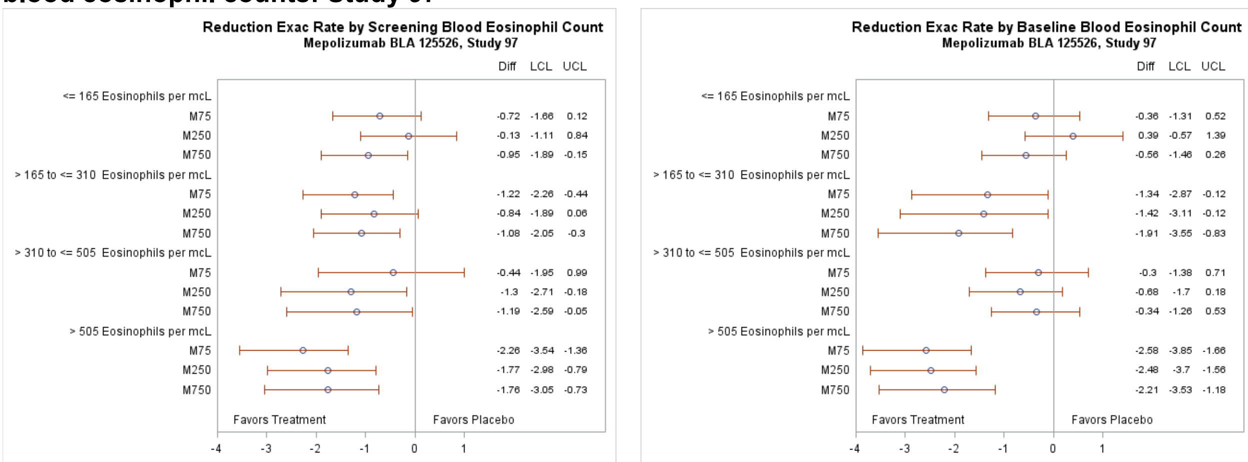
This is in contrast to an initial proof-of-concept study evaluating a pilot formulation of mepolizumab in a broader population of asthmatics. Study 06, discussed in Section 5.1.7, failed to demonstrate a lung function benefit in less severe asthma, despite a reduction in blood eosinophils[17]. However, further evaluation in an investigator-sponsored study of mepolizumab in 61 patients with a history of at least 2 exacerbations requiring oral steroids and elevated sputum eosinophil counts > 3% on at least one occasion in the previous 2 years provided initial proof-of-concept support that mepolizumab decreased the number exacerbations in a more selective patient population[18].

Subsequently, the sponsor conducted Study 97 using a broader set of inclusion criteria to identify patients with evidence of eosinophilic inflammation. Based on these results, the sponsor further refined the enrichment criteria for eosinophilic inflammation in Studies 88 and 75. Notably, the overall design of the program provides only limited data in patients with severe asthma with an exacerbation history who fail to meet the specific peripheral blood eosinophil thresholds applied in the phase 3 program. Given the available efficacy data to date, it is important to consider the potential role of this product in the current treatment paradigms for asthma and how clinical decisions will be made on whom to treat.

An analysis of exacerbation data by screening and baseline eosinophil count from Studies 97 and 88 by the Agency suggest that the mepolizumab treatment effect increases as an individual's peripheral blood eosinophil count increases (Figure 7, Figure 8).

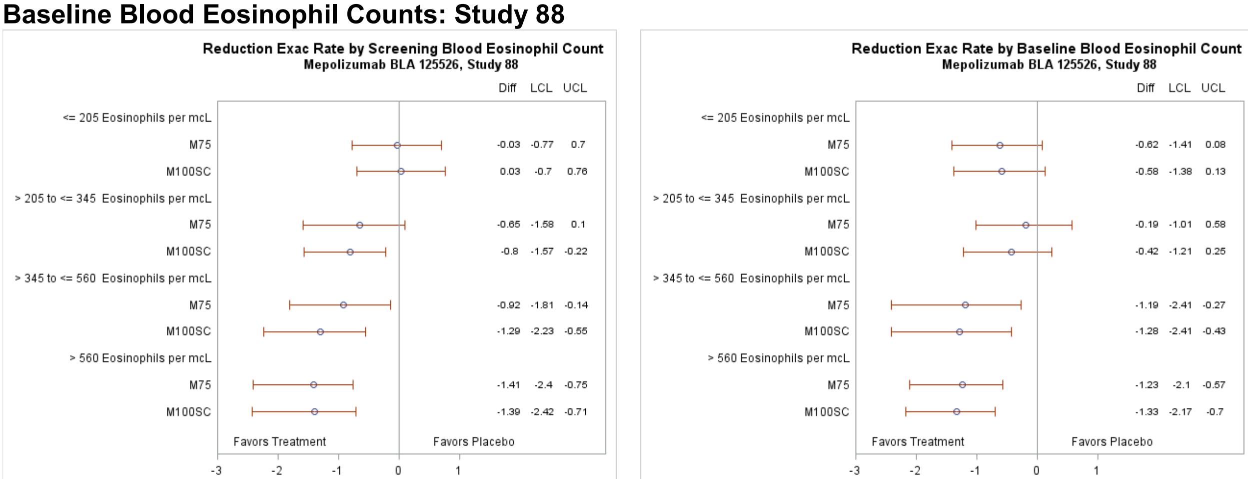
[17] Flood-Page, Patrick, et al. "A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma." American journal of respiratory and critical care medicine 176.11 (2007): 1062-1071.
[18] Haldar, Pranabashis, et al. "Mepolizumab and exacerbations of refractory eosinophilic asthma." *New England Journal of Medicine* 360.10 (2009): 973-984.

Figure 7: Difference between treatment and placebo exacerbation rates, by screening and baseline blood eosinophil counts: Study 97



Source: FDA Statistical Reviewer Analyses

Figure 8: Difference between Treatment and Placebo Exacerbation Rates, by Screening and Baseline Blood Eosinophil Counts: Study 88



Source: FDA Statistical Reviewer Analyses

In addition, the sponsor’s analysis of the exacerbation data from Study 88 categorized by inclusion criteria suggested a trend for greater treatment effect for subjects meeting the eosinophil cutoff at initiation than for subjects enrolled based on a historical value alone (Table 13). However, that trend was not statistically significant, with the analysis possibly hampered by loss of power due to dichotomization of the integer/continuous eosinophil measurement.

Table 13: Exploratory Analyses of the primary endpoint: the annual rate of exacerbations by blood eosinophil inclusion criterion for Study 88

	Placebo N = 191	**Mepo 100 SC**	**Mepo 75 IV**
≥ 300 cells/µL in the previous 12 months <u>OR</u> ≥ 150 cells/µL at screening			
Only met ≥ 150 cells/µL at screening			
N	69	48	59
Rate/year	1.92	0.49	0.54
Only met ≥ 300 cells/µL in prior 12 months			
N	23	39	34
Rate/year	1.53	1.24	1.61
Met both criteria: ≥ 300 cells/ µL in previous 12 months **<u>AND</u>** ≥ 150 cells/µL at screening			
N	98	107	96
rate/year	1.62	0.74	0.97
Source: Study 88 CSR Table 25			

While strong trends are seen for a positive treatment modification effect by peripheral blood eosinophil count, several factors should be considered by the panel when discussing how the eosinophil data from this program should be used to inform appropriate use of mepolizumab in clinical practice.

First, peripheral blood eosinophil counts are not static measurements with respect to time. Several publications have documented the variability in counts obtained within an individual in a single day as well as over time[19,20,21]. This finding is further substantiated by data from this program which provided both screening and baseline peripheral blood eosinophil counts in individual subjects. The Agency's statisticians evaluated these data for Studies 97[22] and 88[23] and found that 34% of individuals in Study 97 crossed above the sponsor's 150 cells/µl threshold between the two measurements with similar variability in counts seen in Study 88.

A second factor to consider is that while a complete blood cell count (CBC) with differentiation is a standard and widely available clinical laboratory test, there is an inherent imprecision in the obtained measurements, particularly for automated counters.

[19] Acland JD, Gould AH. Normal variation in the count of circulating eosinophils in man. J Physiol 1956; 133:456–466.
[20] Spector, Sheldon Laurence, and Ricardo Antonio Tan. "Is a single blood eosinophil count a reliable marker for "eosinophilic asthma?"." *Journal of Asthma* 49.8 (2012): 807-810.
[21] Tatai K, Ogawa S. A study of diurnal variation in circulating eosinophils especially with reference to sleep in healthy individuals. Jpn J Physiol 1951; 1:328–331.
[22] Screening and baseline values were obtained 1 to 6 weeks apart
[23] Screening and baseline values were obtained 1 week apart

Use of the central laboratory by this program would limit some of the inter-machine variability that would likely be seen in general clinical practice; although, this use cannot account for any additional imprecision due to intra-machine variability. Thus, the generalizability of the eosinophil data to a real-world situation is unknown.

Both of these factors speak to an underlying lability in peripheral blood eosinophil measurements. It remains unclear how this variability should be factored into the treatment decision for individual patients. While likely not an issue for those with counts “higher” than those outlined in this sponsor’s development program, the treatment decision is less clear for those with borderline “low” values with respect to the sponsor’s inclusion criteria.

Finally, the heterogeneity of severe asthma must be considered. As shown in Table 14, additional factors such sputum eosinophilia ≥3%, exhaled nitric oxide ≥ 50 ppb, and deterioration of asthma control following at least a 25% reduction in corticosteroid use, were examined. Numerical beneficial trends for mepolizumab were observed in these subgroups; however no statistically significant interactions between any subgroup and treatment were identified.

Table 14: Exploratory analysis of the primary endpoint: rate of exacerbations by inclusion criterion for Study 97

		Mepolizumab		
	Placebo N=155	**75 IV N=153**	**250 IV N = 152**	**750 IV N=156**
Blood eosinophil ≥ 300 cells/μL related to asthma*				
N	96	85	93	91
Exacerbation rate per year	2.22	1.08	1.16	1.22
Sputum eosinophilia ≥ 3%*				
N	16	18	16	14
Exacerbation rate per year	2.03	1.13	0.96	1.40
Exhaled nitric oxide ≥ 50 ppb*				
N	70	61	57	74
Exacerbation rate per year	2.83	1.25	1.5	0.92
Deterioration of asthma control following at least a 25% reduction in corticosteroid use*				
N	48	46	41	47
Exacerbation rate per year	2.57	1.04	1.48	0.88

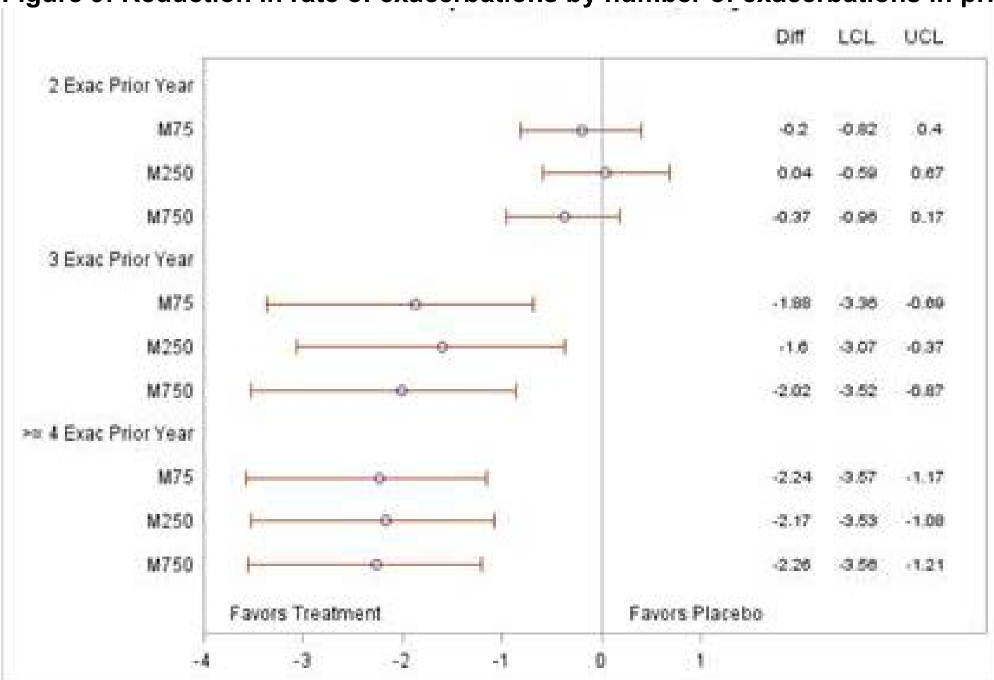
Source: Study 97 CSR Table 11
* Tests for treatment by subgroup interaction each are not statistically significant

An exploratory analysis by the Agency suggests a numerical trend towards an increased treatment response as a patient’s exacerbation history increases (Figure 9 and Figure 10); however, this relationship is uncertain in that the treatment-by-number-of- previous-exacerbations is not significant (Study 97 p=0.067, Study 88 p=0.42).

Notably, the number of exacerbations in the previous year is a component of the ATS/ERS guidelines for severe asthma, suggesting that meeting criteria for a severe asthma diagnosis may be sufficiently predicative of a treatment response in some individuals.

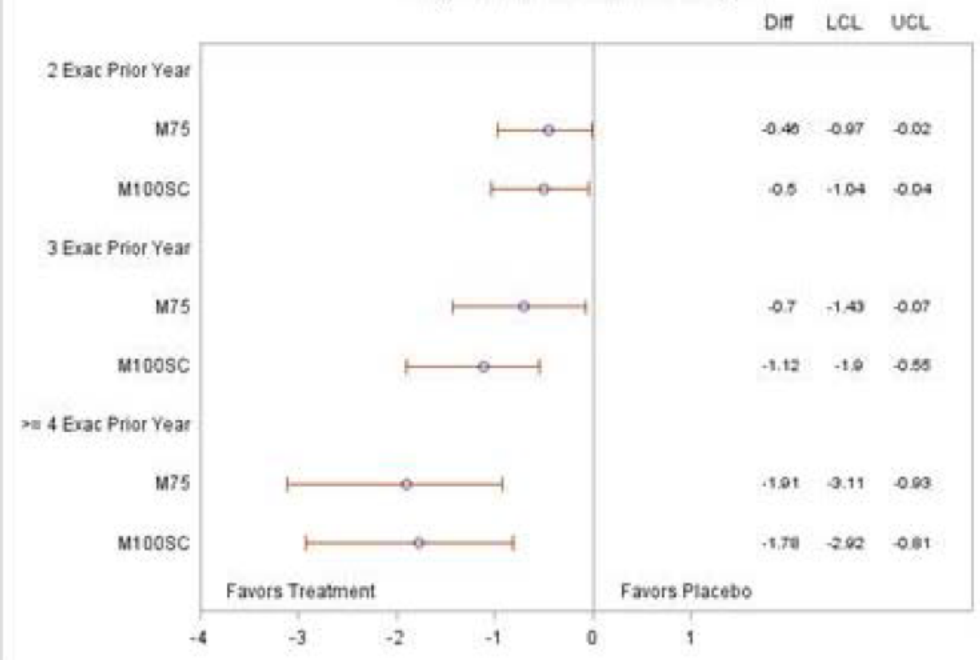
Analysis by the Agency also evaluated the effect of other potential treatment modifiers (including screening FEV1 reversibility, FENO, baseline percent predicated FEV1, and ACQ). None of these factors appeared to impact the treatment effect (data not shown).

Figure 9: Reduction in rate of exacerbations by number of exacerbations in prior year: Study 97



Source: FDA Statistical Reviewer Analysis

Figure 10: Reduction in exacerbation rate by exacerbations in prior year: Study 88



Source: FDA Statistical Reviewer Analysis

Additional sensitivity analyses of exacerbation data: Studies 97, 88

<u>Exacerbations requiring hospitalizations or ER visit and exacerbations requiring hospitalization: Studies 97 and 88</u>

While overall rates are low, the data for exacerbations requiring hospitalization or ER visit or hospitalization alone are consistent with the primary endpoint (Table 15). Similar trends are seen in Study 75 (data not shown).

Table 15: Rate of exacerbations requiring hospitalization or ER visit or hospitalization alone: Studies 97 and 88

		Mepolizumab			
	Placebo	**100 SC**	**75 IV**	**250 IV**	**750 IV**
Study 97					
Exacerbations requiring hospitalization or ER visit					
N	155	--	153	152	156
Rate per year	0.43	--	0.17	0.25	0.22
Exacerbations requiring hospitalization					
N	155	--	153	152	156
Rate per year	0.18	--	0.11	0.12	0.07
Study 88					
Exacerbations requiring hospitalization of ER visit					

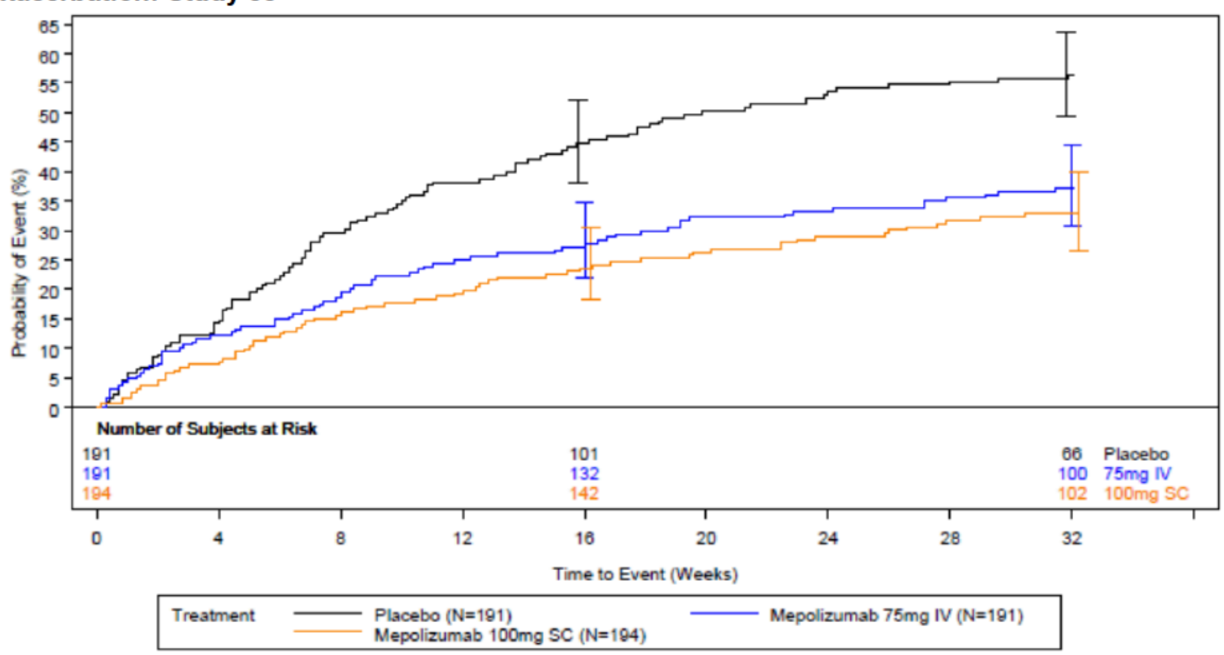
		Mepolizumab			
	Placebo	100 SC	75 IV	250 IV	750 IV
N	191	194	191	--	--
Rate per year	0.20	0.08	0.14	--	--
Exacerbations requiring hospitalization					
N	191	194	191	--	--
Rate per year	0.10	0.03	0.06	--	--
Source: FDA Statistical Reviewer Analysis					

Time to First Exacerbation: Studies 97, 88

Consistent with the primary endpoint, mepolizumab treated subjects demonstrated an increased time to first exacerbation in Studies 97 and 88 (Figure 11, Figure 12).

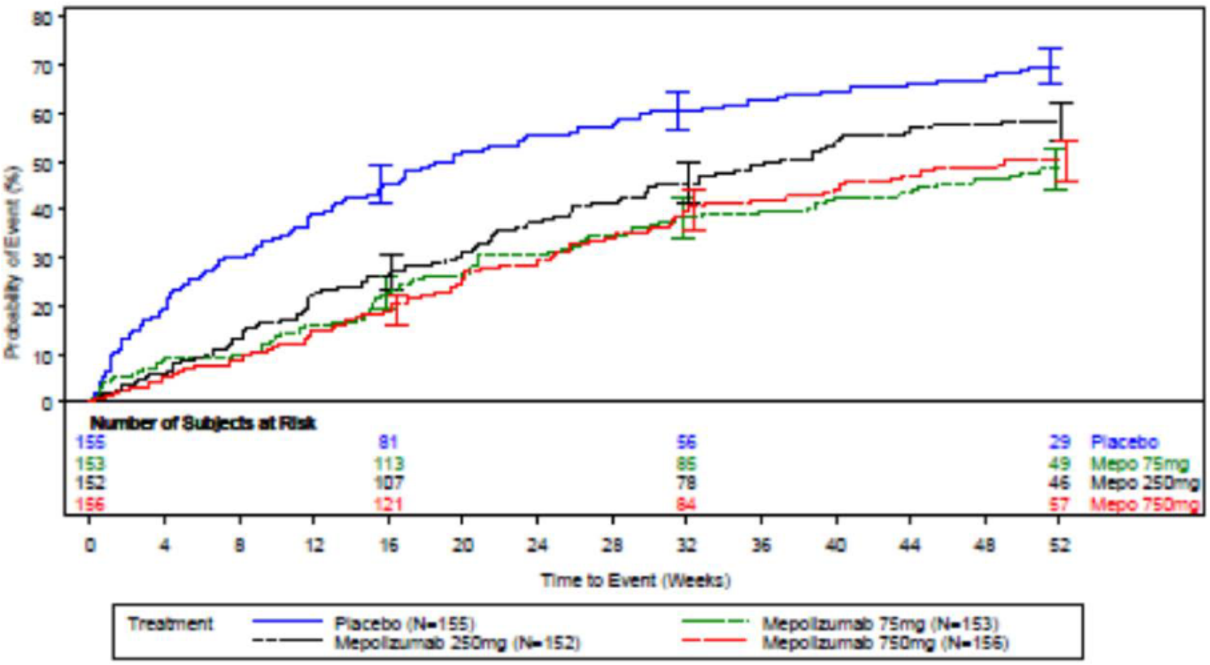
Similar trends in both studies are seen for the time to first exacerbation requiring hospitalization or ER visit and time to first exacerbation requiring hospitalization (data not shown).

Figure 11: Kaplan-Meier cumulative incidence curve for time to first clinically significant exacerbation: Study 88



Source: Study 88 CSR Figure 4

Figure 12: Kaplan-Meier cumulative incidence curve for time to first clinically significant exacerbation: Study 97



Source: Study 97 CSR Figure 6.06

<u>Oral Corticosteroid Use Associated with an Exacerbation: Studies 97, 88</u>

Consistent with the primary endpoint, mepolizumab treated subjects had fewer CS significant exacerbations treated with OCS than placebo treated subjects. However, the average number of days of OCS treatment per exacerbation was similar to slightly lower for placebo-treated subjects compared to those treated with mepolizumab (Table 16). Thus, while mepolizumab may decrease the number of exacerbations, it does not appear to impact the length of time clinicians used OCS to treat the exacerbations.

Table 16: Summary of number of days with oral corticosteroids associated with an exacerbation: Studies 97 and 88

		Mepolizumab			
	Placebo	**100SC**	**75 IV**	**250 IV**	**750 IV**
Study 97					
N	155	--	153	152	156
Number of exacerbations treated with OCS	276		145	177	148
Mean number of days with OCS use per exacerbation	13.1	--	14.2	11.2	14.5

Study 88					
N	191	194	191	--	--
Number of exacerbations treated with OCS	208	103	107		
Mean number of days with OCS use per exacerbation,	10.4	11.1	11.1	--	--
Source: Study 97 CSR Table 30; Study 88 CSR Table 36, Table 37					

5.1.4.2 Oral Corticosteroid (OCS) Percent Reduction from Baseline during Weeks 20-24 by Reduction Categories: Study 75

While the impact on exacerbations was the primary focus of Studies 97 and 88, Study 75 employed a different primary endpoint to evaluate the efficacy of mepolizumab treatment. This OCS withdrawal study evaluated the effect of the mepolizumab dose/route proposed for marketing on OCS withdrawal without loss of asthma control.

Similar to Studies 97 and 75, mepolizumab treatment demonstrated a statistically significant treatment effect. Mepolizumab treated subjects demonstrated a statistically significant increased odds of achieving a greater average percent reduction from baseline OCS dose while maintaining asthma control than subjects in the placebo treatment arm (Table 17).

Table 17: Percent reduction in OCS dose during weeks 20-24: Study 75

	Placebo N = 66	**Mepo100 SC N=69**
% reduction from baseline (n, %)		
90% - 100%	7 (11)	16 (23)
75% - < 90%	5 (8)	12 (17)
50% - < 75%	10 (15)	9 (13)
> 0% - < 50%	7 (11)	7 (10)
No change or increase or lack of asthma control or withdrawal from treatment	37 (56)	25 (36)
Odds Ratio to placebo	--	2.39
P value	--	0.0085
Source: FDA Statistical Review Table 14		

Additional analyses of the OCS reduction data from this study are summarized below.

OCS Reduction from Baseline during Weeks 20-24: Study 75
Overall, these data support the primary endpoint for Study 75. Mepolizumab treatment allowed just over half of treated subjects to titrate to a dose of OCS ≤ 5 mg and 14% to

titrate off OCS completely compared to 32% and 8% of placebo treated subjects. Given the chronicity with which many subjects required OCS dosing, complete off-titration of steroids may not have been possible during the treatment phase given HPA axis concerns.

Table 18: Exploratory endpoints for OCS reduction: Study 75

	Placebo N = 66	Mepo 100 SC N = 69
50% – 100% of baseline	33%	54%
Total reduction of OCS dose (to 0 mg)	8%	14%
Reduction in daily OCS dose ≤ 5mg, n %	32%	54%
Median Dose, mg	10	3.1
Median % reduction from baseline	0%	50%
Source: FDA Statistical Reviewer Analysis		

OCS Reduction over Time

Both mepolizumab and placebo treated subjects demonstrated a reduction in OCS dosing by Week 4-8. Consistent with the primary endpoint, mepolizumab treated subjects demonstrated a consistently greater percent reduction over time than placebo treated subjects.

Table 19: OCS reduction over time: Study 75

	Placebo N = 66		Mepo 100 SC N = 69	
	Daily dose (mg)	% reduction from baseline	Daily Dose (mg)	% reduction from baseline
Baseline	12.5	--	10	--
Week 0–4	12.5	0	20	0
Week 4-8	10	10.8	8.5	30.4
Week 8-12	10	20	5.7	40.0
Week 12-16	10	14.8	5.4	47.3
Week 16-20	10	22.5	5.0	54.0
Week 20-24	10	20	3.1	66.7
Source: Study 75 CSR Table 19				

The sponsor provided additional subgroup analyses of the primary endpoint taking into consideration duration of prior OCS use, baseline OCS dose and baseline eosinophil count. These are summarized in Table 20. The limitations of the small sample sizes should be kept in mind when considering these data.

Table 20: Exploratory analyses of the primary endpoint: percent reduction in OCS dose from baseline during weeks 20-24: Study 75

	Placebo N = 66	Mepo100 SC N=69
DURATION OF PRIOR OCS USE		
< 5 years of OCS use at baseline		
N	35	35
90% - 100 %	4 (11)	9 (26)
75% - < 90%	3 (9)	1 (3)
50% - < 75%	2 (6)	8 (23)
> 0% - < 50%	3 (9)	3 (9)
No change or increase or lack of asthma control or withdrawal from treatment	23 (66)	14 (40)
≥ 5 years of OCS use at baseline		
N	31	34
90% - 100 %	3 (10)	7 (21)
75% - < 90%	2 (6)	11 (32)
50% - < 75%	8 (26)	1 (3)
> 0% - < 50%	4 (13)	4 (12)
No change or increase or lack of asthma control or withdrawal from treatment	14 (45)	11 (32)
BASELINE OCS DOSE		
5 mg to < 10 mg		
N	17	22
90% - 100 %	4 (24)	7 (32)
75% - < 90%	0	5 (23)
50% - < 75%	4 (24)	3 (14)
> 0% - < 50%	0	1 (5)
No change or increase or lack of asthma control or withdrawal from treatment	9 (53)	6 (27)
10 < 15 mg		
N	22	28
90% - 100 %	3 (14)	7 (25)
75% - < 90%	4 (18)	5 (18)
50% - < 75%	4 (18)	2 (7)
> 0% - < 50%	3 (14)	3 (11)
No change or increase or lack of asthma control or withdrawal from treatment	8 (36)	11 (39)
≥ 15 mg		
N	27	19
90% - 100 %	0	2 (11)
75% - < 90%	1 (4)	2 (11)
50% - < 75%	2 (7)	4 (21)
> 0% - < 50%	4 (15)	3 (16)

	Placebo N = 66	Mepo100 SC N=69
No change or increase or lack of asthma control or withdrawal from treatment	20 (74)	8 (42)
BASELINE EOSINOPHIL LEVEL < 150 cells/µL		
N	18	15
90% - 100 %	1 (6)	6 (40)
75% - < 90%	0	3 (20)
50% - < 75%	3 (17)	2 (13)
> 0% - < 50%	3 (17)	1 (7)
No change or increase or lack of asthma control or withdrawal from treatment	11 (61)	3 (20)
150 to < 300 cells/µL		
N	20	18
90% - 100 %	3 (15)	4 (22)
75% - < 90%	2 (10)	2 (11)
50% - < 75%	2 (10)	2 (11)
> 0% - < 50%	1 (5)	1 (6)
No change or increase or lack of asthma control or withdrawal from treatment	12 (60)	9 (50)
300 to < 500 cells/µL		
N	9	16
90% - 100 %	1 (11)	3 (19)
75% - < 90%	1 (11)	4 (25)
50% - < 75%	1 (11)	3 (19)
> 0% - < 50%	1 (11)	1 (6)
No change or increase or lack of asthma control or withdrawal from treatment	5 (56)	5 (31)
≥ 500 cells/µL		
N	19	20
90% - 100 %	2 (11)	3 (15)
75% - < 90%	2 (11)	3 (15)
50% - < 75%	4 (21)	2 (10)
> 0% - < 50%	2 (11)	4 (20)
No change or increase or lack of asthma control or withdrawal from treatment	9 (47)	8 (40)
Source: Study 75 CSR Tables 20, 21, 23		

5.1.5 Additional Efficacy Analyses

The sponsor evaluated multiple secondary endpoints in each of its pivotal efficacy and safety studies. Although statistically significant results were not shown for these secondary endpoints, the results trend in support of efficacy for mepolizumab.

Table 21: Summary of statistical hierarchal testing procedure: Studies 97, 88

	Ordering of the secondary endpoints for multiplicity adjustment
Study 97	• Rate of exacerbations • FEV1 pre-bronchodilator at week 52 • AQLQ at week 52 • Rate of exacerbations requiring hospitalizations or ED visit • ACQ at week 52
Study 88	• Rate of asthma exacerbations • Frequency of exacerbations requiring hospitalization (including intubation and admittance to an ICU) or ED visit • Frequency of exacerbations requiring hospitalization • Mean change from baseline in clinic pre-bronchodilator FEV_1 • Mean change in St. George's Respiratory Questionnaire
Study 75	• No adjustment for multiplicity was made for the secondary endpoints. The analyses of the secondary endpoints were to be considered sensitivity analyses.
Source: Study 97 CSR page 52, study 88 CSR page 102	

While the frequency of exacerbations requiring hospitalization, or hospitalization/ED visit were officially designated as secondary endpoints in Studies 97 and 88, and the OCS use with each exacerbation were designated as “other endpoints”, these results are discussed as exploratory analyses in the discussion of the primary endpoint data of this briefing document.

Of note, no adjustments for multiplicity were made for any of the secondary endpoints evaluated in Study 75. These data were considered by the sponsor to be exploratory analyses in support of the primary endpoint.

Lung Function: Studies 97, 88 and 75

While the effect on lung function was not a primary efficacy variable for any of the pivotal efficacy studies, evaluation of a treatment effect on lung function is an important consideration in any asthma program.

The change from baseline in pre-bronchodilator FEV1 at Week 52 and Week 32 were designated as secondary endpoints in Studies 97 and 88, respectively. The evaluation of lung function data in Study 75 was designated as an “other endpoint”.

No consistent improvement over placebo in trough FEV1 is seen in Study 97. However, in Studies 88 and 75, numeric treatment benefits of approximately 100 ml in the mepolizumab 100 mg SC treatment groups compared to placebo are seen in the trough FEV1 data. Although these results are not statistically significant, the 100 ml improvement is in addition to background standard of care therapy which for > 93% of the study population included ICS/LABA therapy (Figure 13, Figure 14, and Figure 15; Table 10).

For Study 97, a small, non-statistically significant, treatment difference between mepolizumab-treated subjects and placebo for trough FEV1 is seen at Week 52 (mepolizumab 75 IV: 61 ml 95%CI [-39, 161]; mepolizumab 250 mg IV 81 ml, 95%CI [-19, 180]; and mepolizumab 750mg IV: 56 ml, 95%CI [-43, 155]). However, similar differences from placebo are not seen earlier in the study. Some of this positive treatment difference may be due to a loss of FEV1 benefit seen over time in the placebo group. Conversely, the lack of mepolizumab treatment effect may be due an unanticipated FEV1 benefit seen in placebo + standard of care treatment group and may reflect the benefits of enrolment in a clinical study (Figure 13).

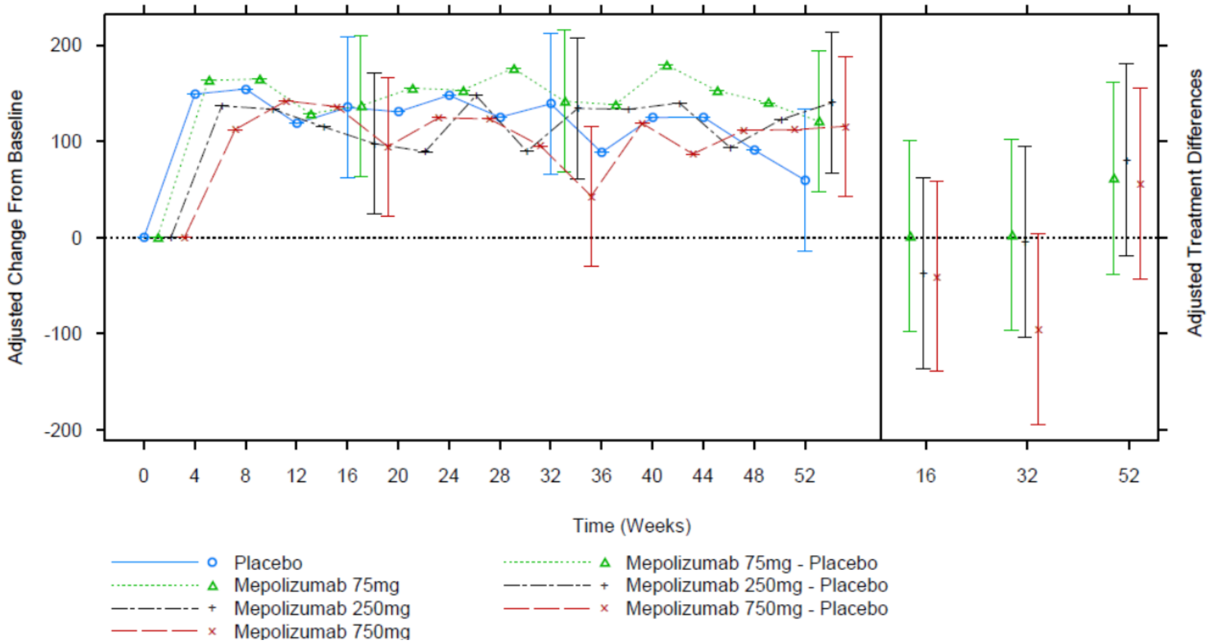
For Study 88, the point estimate at Week 32 demonstrates a 98 ml (95% CI 11, 184) and 100 ml improvement (95% CI 13, 187) in the change from baseline over placebo for the 100 mg SC and 75 mg IV treatment arms respectively. In this study, the placebo group did demonstrate some improvement from baseline in pre-bronchodilator FEV1; however, the improvement was not as profound as in Study 97, and the mepolizumab treatment arm consistently demonstrated numeric improvement compared to placebo across all timepoints.

For Study 75, numeric improvements from placebo are seen at Week 24 (114 ml improvement; 95% CI 42, 271; Figure 15). In contrast to Studies 97 and 88, the placebo group failed to demonstrate any improvement from baseline.

The difference in the placebo response between the three studies remains unclear, although the lack of placebo effect in Study 75 may be due, in part, to the OCS withdrawal built into the study design.

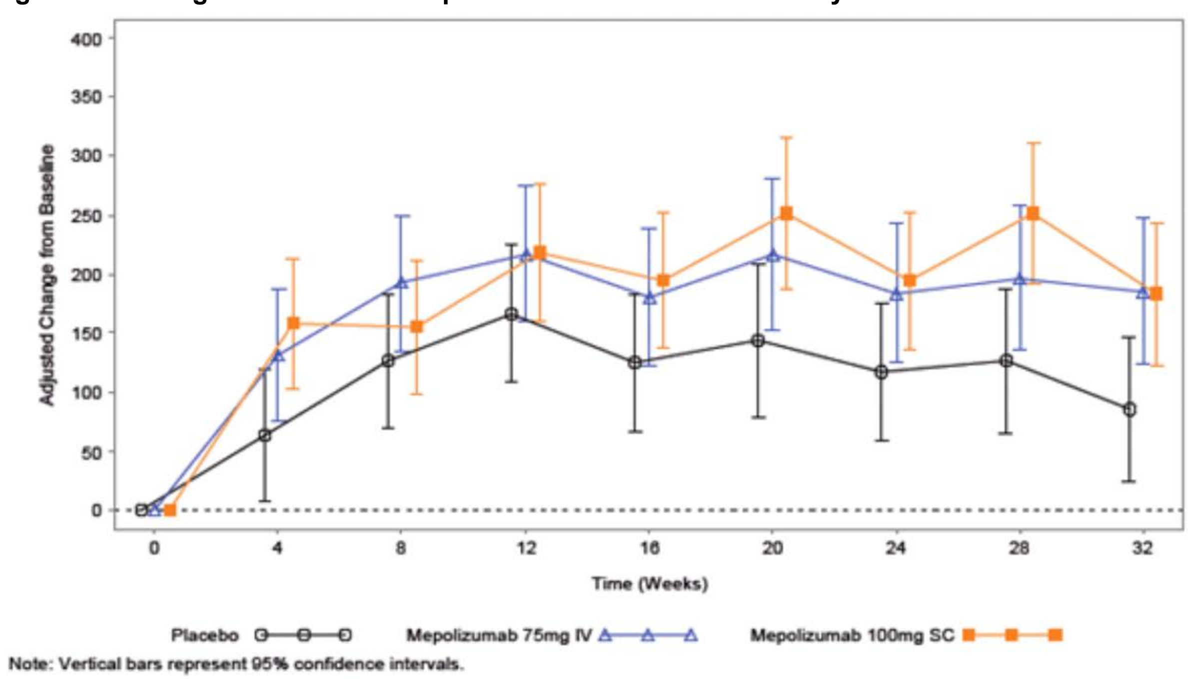
Similar data are seen for the evaluation of post-bronchodilator FEV1 (data not shown).

Figure 13: Change from baseline in pre-bronchodilator FEV1 (ml): Study 97



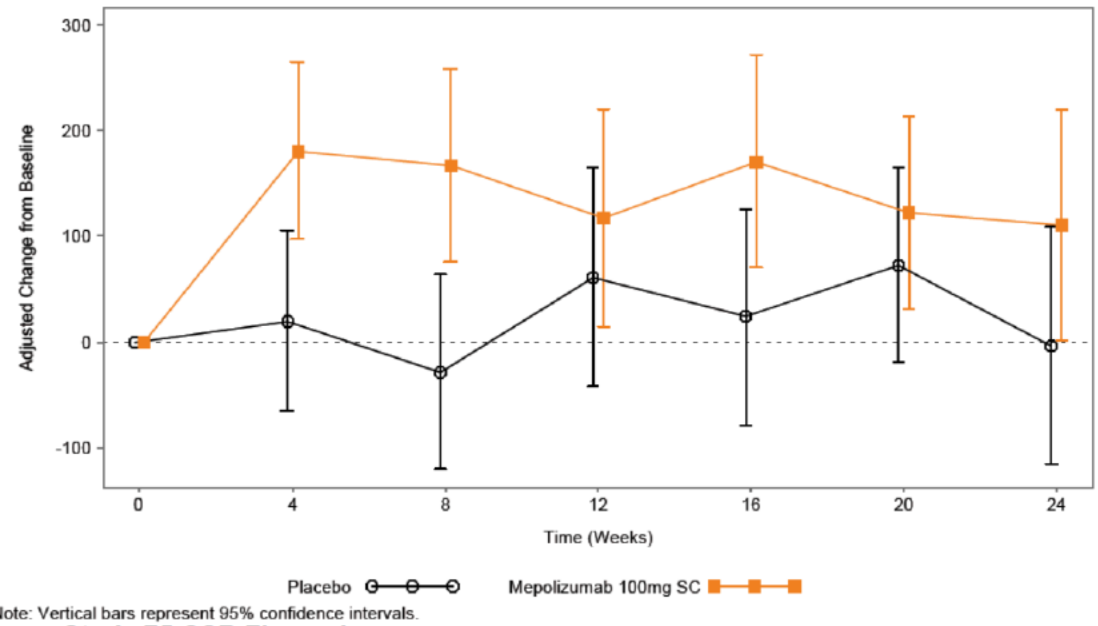
Source: Study 97 CSR Figure 7

Figure 14: Change from baseline in pre-bronchodilator FEV1: Study 88



Source: Study 88 CSR Figure 8

Figure 15: Change from baseline in pre-bronchodilator FEV1: Study 75



Source: Study 75 CSR Figure 4

<u>SGRQ: Studies 88 and 75</u>

SGRQ was assessed in Studies 88 and 75, but not in Study 97. In both studies, a greater decrease in SGRQ was observed for the mepolizumab treatment groups compared to placebo at the end of treatment. Differences from baseline as well as differences from placebo exceed the established minimally clinically important difference (MCID) of 4 (Table 22). While the data are suggestive of a positive treatment effect, results are only nominally significant due to failure within the testing hierarchy for Study 88 and failure to account for multiplicity in Study 75.

In Study 88, it is notable that the change from baseline in the placebo group also exceeds the MCID of 4; however the difference in the change from baseline between the mepolizumab treatment groups and placebo also exceeds 4, suggesting a positive mepolizumab treatment effect on this endpoint.

Similar to the total score, greater improvements for mepolizumab treated groups over placebo are seen for the individual domains comprising the total score (data not shown).

Table 22: Exploratory Analysis SGRQ mean total score: Study 88 and Study 75

	Placebo	**Mepo 100**	**Mepo 75**
Study 88			
Baseline	46.9	47.9	44.4
Week 32	38	31.5	30.2
LS mean change from baseline	-9	-16	-15

	Placebo	Mepo 100	Mepo 75
95% CI	-11, -7	-18, -13	-18, -14
Difference from placebo	--	-7.0	-6.4
95% CI	--	-10.2, -3.8	-9.7,-3.2
Study 75			
N	66	69	--
Baseline	45	49.6	--
Week 24	42.1	40.6	--
LS mean change from baseline	-3	-9	--
95% CI	-7,0	-13,-5	--
Difference from placebo	--	-5.8	--
95% CI	--	-10.6,-1.0	--
Source: Statistical Review Table 16 and Study 88 CSR Tables 6.47 and 6.49, Study 75 Tables 6.32, 34			

ACQ score: Studies 97, 88, 75

Numeric improvements in ACQ were demonstrated for mepolizumab treated subjects in Studies 97, 88, and 75. Again, results are nominally significant only either due to failure in the statistical testing hierarchy or failure to account for multiplicity.

Table 23: Exploratory Analysis: Mean change from baseline in ACQ Score: Studies 97, 88

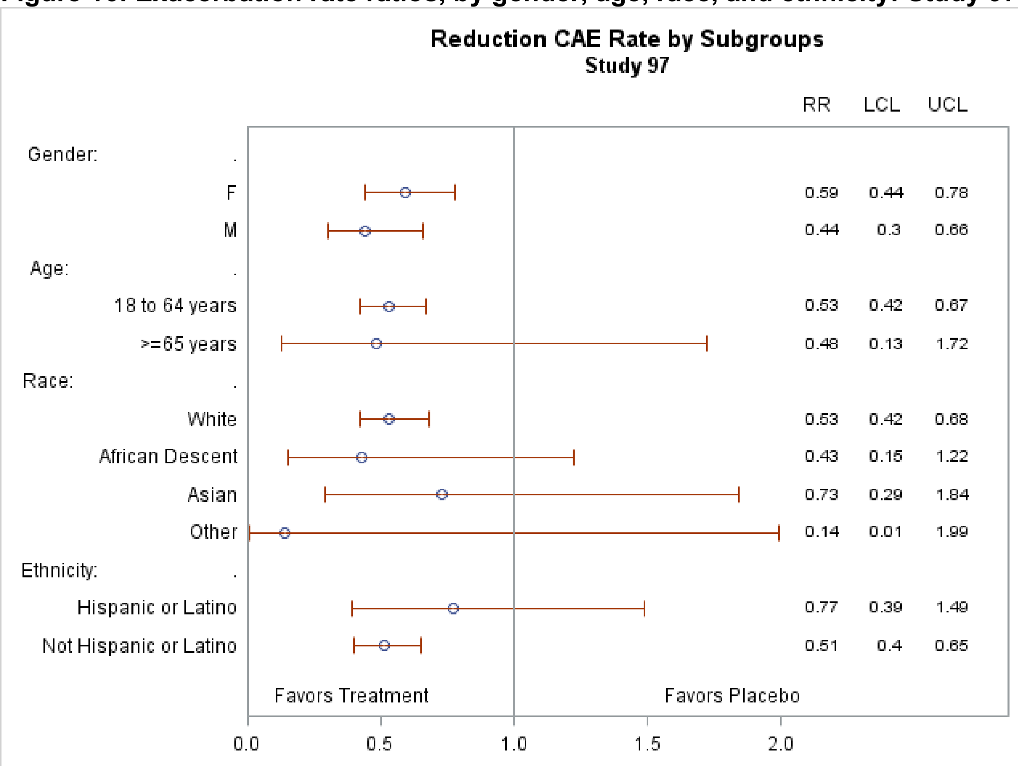
		Mepolizumab			
	Placebo	100 SC	75 IV	250 IV	750 IV
Study 97: Week 52					
LS mean Δ from baseline	-0.59	--	-0.75	-0.87	-0.80
Difference from placebo	--	--	-0.16	-0.27	-0.20
95% CI	--	--	-0.39,0.07	-0.51,-0.04	-0.43,0.03
Study 88: Week 32					
LS mean Δ from baseline	-0.50	-0.94	-0.92	--	--
Difference from placebo	--	-0.44	-0.42	--	--
95% CI	--	-0.63,-0.25	-0.61,-0.23	--	--
Study 75: Week 24					
LS mean Δ from baseline	-0.09	-0.61			
Difference from placebo	--	-0.52			
95% CI		-0.87,-0.17			
Source: Study 97 CSR Table 6.47, Study 88 CSR Table 4, Study 75 Table 32					

5.1.6 Subpopulations

The Agency's statistical review provided a subgroup analyses of the efficacy data by gender, age, race and ethnicity. All mepolizumab doses were pooled in these analyses to increase the sample size.

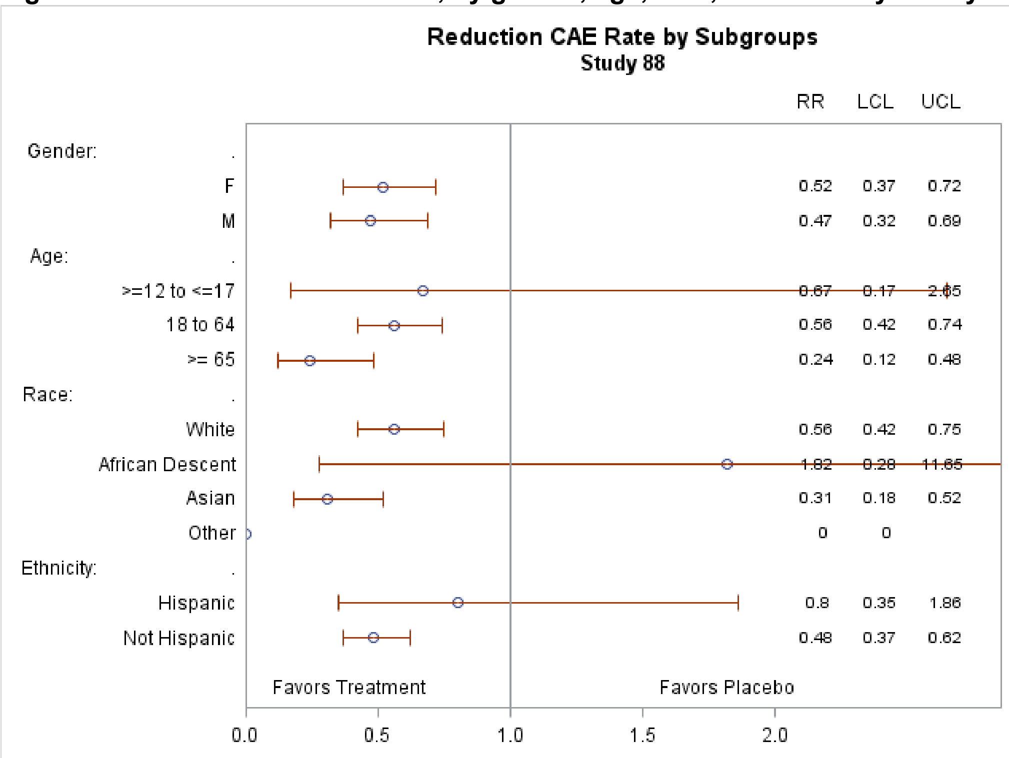
While the data for the most subgroups trend in the appropriate favorable direction for mepolizumab, the impact of the limited data is evident in the wide confidence intervals. These data are summarized in Figure 16, Figure 17, and Figure 18. Of note the adolescent subgroup is missing from Studies 97 and 75 as only one adolescent was enrolled in Study 97 and no adolescents were enrolled in Study 75. Similarly, an analysis in subjects of African descent is missing from Study 75 as this study did not enroll any subjects in this subgroup.

Figure 16: Exacerbation rate ratios, by gender, age, race, and ethnicity: Study 97



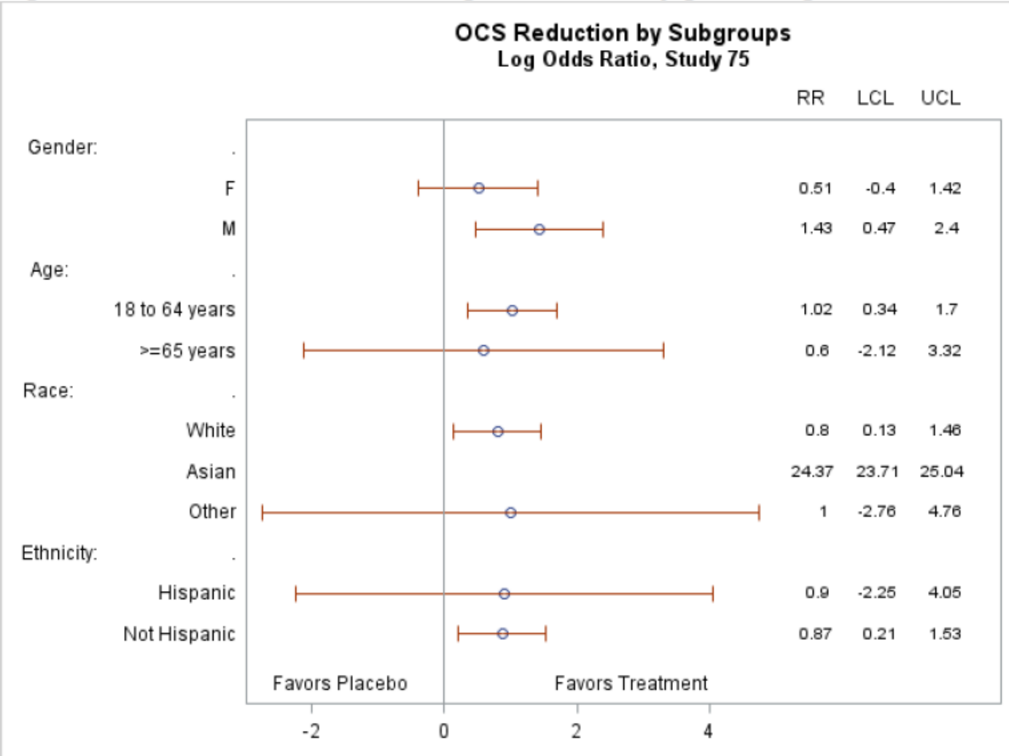
Source: FDA Statistical reviewer Analysis

Figure 17. Exacerbation rate ratios, by gender, age, race, and ethnicity: Study 88



Source: FDA Statistical reviewer Analysis

Figure 18. Exacerbation reduction log odds ratios, by gender, age, race, and ethnicity: Study 75



Source: FDA Statistical Reviewer Analysis

Adolescents
As noted above, the rate ratio for adolescent subjects trend in a favorable direction in Study 88; although there is a limited quantity of data.

Figure 17 represents pooled data for all of the evaluated mepolizumab doses. Pooling the data from these doses is not unreasonable as the 75 mg IV and 100 mg SC treatment arms have similar systemic exposure and a similar magnitude of a treatment effect was demonstrated in the whole population. Table 24 summarizes the adolescent exacerbation data from Study 88 in tabular format providing a breakdown by dose. When this is done, a trend towards a positive treatment effect is no longer seen.

Table 24: Summary of exacerbation data for adolescents age 12 to 17 years old and for subjects ≥ 18 years of age: Study 88

	Placebo	Mepo 100 SC	Mepo 75 IV
12 to 17 years of age			
N	9	7	9
≥ 1 exacerbation (%)	3 (33)	0	3 (33)
Rate/year	0.92	0	1.12
Difference from placebo	--	-0.92	0.2
≥ 18 years of age			
N	182	187	182

Rate/year	1.79	0.85	0.92
Difference from placebo	--	-0.94	-0.87
Source: FDA Statistical Reviewer Analysis Study 88 CSR Table 6.75			

To provide further contextual information regarding the efficacy of mepolizumab in the pediatric population, the statistical team provided an analysis using an arbitrary cutoff of 40 years. Interestingly, when the OCS reduction data from Study 75 are evaluated using this age cutoff, the data indicate that the OCS reduction treatment effect is lost in the 'younger' asthmatic patients (Table 25). However, similar results were not seen for the exacerbation data in Studies 97 and 88.

Table 25: Percent OCS reduction for subjects older and younger than 40 years of age: Study 75

	< 40 years		**≥ 40 years**	
	Placebo N = 12	**Mepo 100 SC N = 18**	**Placebo N = 54**	**Mepo 100 SC N = 51**
90%-100%	4 (33)	1 (6)	3 (6)	15 (29)
75% - <90%	0 (0)	3 (17)	5 (9)	9 (18)
50% -<75%	4 (33)	3 (17)	6 (11)	6 (12)
>0% - < 50%	1 (8)	1 (6)	6 (11)	6 (12)
No change of any increase or lack of asthma control or withdrawal from treatment	3 (25)	10 (56)	34 (63)	15 (29)
Source: FDA Statistical Reviewer Analysis				

Given the novelty of the targeted patient population for this therapy, the Agency is interested in hearing the panel's thoughts on the relevance of the enrolled population in the pediatric population. This is of particular importance as the development program enrolled relatively few adolescent subjects making it difficult to drawn firm conclusions regarding efficacy of the product. Whether the available adolescent data are sufficient to warrant approval in this age group will be a topic for discussion by the members of the advisory committee. Should the panel feel that the severe asthma phenotype with a characteristic blood eosinophil pattern is the same disease in adolescents and adults, partial extrapolation of the efficacy data from the adult to adolescents may not be unreasonable. However, if questions remain regarding the relevance of this phenotype to the pediatric population, additional studies may be warranted.

As this application triggers the Pediatric Research Equity Act (PREA), the Agency has the regulatory authority to require additional study(ies) in the pediatric population including further evaluation in the adolescent population (12-17 years old) and younger.

Race and Ethnicity

Given the increased asthma morbidity and mortality seen in African American patients with asthma[24], the subgroup analysis and the adequacy of the available data for this patient population is also of particular interest to the Agency.

Table 26 and Table 27 provide a comparison of the enrolled patient population compared to the expected percentage of the US population for the racial and ethnic subgroups as well as adolescents. Using data from the CDC and Schatz et al, 2015, the statistical team's analysis attempted to account for the asthma severity including exacerbation history to generate the expected percentage of US population.

Table 26 provides the data from the global study population in its entirety, while Table 27 provides the percentage relative to the study population enrolled from the United States. As would be expected in multinational clinical development programs, the enrolled population of African Americans is markedly smaller than what would expected from the US population. However, when considering only the percentage of the enrolled population from the United States, African Americans are enrolled in similar to expected numbers for Studies 97 and 88.

Table 26: Samples sizes, actual and expected for selected subgroups: Studies 97, 88, 75

	Study			Expected US[1]
	97	88	75	
Randomized, N	616	576	135	--
African Descent, n (%)	24 (4)	16 (3)	0	--
American of African Descent, n (%)	22 (4)	14 (2)	0	18%
Asian, n (%)	34 (6)	105 (18)	3 (2)	5%
Hispanic, n (%)	61 (10)	51 (9)	5 (4)	14%
12 to 17 years of age, n (%)	1 (<1)	25 (4)	2 (1)	9%

[1] Number expected in United States calculated as Prob(Subgroup|Asthma with ≥ 2 exacerbations,USA) = Prob (Asthma with ≥ 2 exacerbations| Subgroup,USA) * Prob(Subgroup |USA) / Prob(Asthma with ≥ 2 exacerbations | USA) Sources of data: www.census.gov/quickfacts/table/PST045214/00, Schatz et al. 2014. The Journal of Allergy and Clinical Immunology: In Practice.Vol 2, Number 5, www.cdc.gov/asthma/most_recent_data.htm. Poisson distribution assumed.
Source: FDA Statistical Reviewer Analysis

Table 27: Sample sizes, actual and expected: Studies 97, 88 and 75

	Study			Expected US[1]
	97	88	75	
Randomized with the USA	78	67	7	18%
American of African Descent, n (%)	22 (28)	14 (21)	0	18%
Asian, n (%)	1 (1)	1 (1)	0	5%

[24] SilverS, Stacy K., and David M. Lang. "Asthma in African Americans: What can we do about the higher rates of disease?." Cleveland Clinic journal of medicine 79.3 (2012): 193-201.

Hispanic, n (%)	6 (8)	5 (7)	0	14%
12 to 17 years of age, n (%)	1 (1)	4 (6)	0	9%
Source: FDA Statistical Reviewer Analysis				

As can be seen in Figure 16 and Figure 17 the efficacy data for patients of African Descent trends in the appropriate direction for Study 97 but not for Study 88; wide confidence intervals are noted for both. Again, there are no data on this subgroup in Study 75. As noted earlier, the Agency is interested in the panel discussion regarding the adequacy of the data obtained in African American subjects given the limited enrolment of this subgroup in the studies, conflicting trends from Studies 97 and 88 and the increased disease burden that African American patients carry with regards to asthma morbidity and mortality in the United States.

Efficacy trends in the appropriate direction for Hispanic and Asian subjects in all three studies.

By Region and Gender

Analysis of the exacerbation data by gender does not reveal any major efficacy concerns (Figure 16 , Figure 17, Figure 18). Likewise, no major differences are noted for the analyses by region (data not shown).

5.1.7 Additional Efficacy Studies

To demonstrate the lack of treatment benefit in subjects with less severe asthma, the sponsor provided the results of Study 06.

Study 06 was a Phase 2, randomized, parallel-group, double-blind, placebo-controlled, multinational, 12-week study. Of note, this study used an earlier pilot formulation of mepolizumab for which there is no PK bridge to the current proposed product. The impact of this change and any differences between the products are unknown.

A total of 362 asthmatic subjects were enrolled. No adolescent subjects were enrolled in this study. Subjects were required to have a FEV1 ≥ 50% and ≤ 80% predicted with demonstrated reversibility ≥ 12%. Prior treatment with an inhaled corticosteroid dose up to a maximum of 1000 mcg/day of beclomethasone or equivalent was allowed.

After a 4-week run-in, eligible subjects were randomized 1:1:1 to receive mepolizumab 250 mg IV, mepolizumab 750 mg IV or placebo. The 12-week treatment period was followed by an 8-week follow-up period. The primary endpoint was the change from baseline of the mean morning domiciliary peak expiratory flow rate recorded in the seven days preceding Week 12. Change from baseline in trough FEV1, asthma symptom score and rescue medication use were evaluated as secondary endpoints.

A total of 362 subjects were randomized with 90% completing the study (97%, 92% and 94% for mepolizumab 750 mg IV, 250 mg IV and placebo respectively). Subjects were predominantly Caucasian (81-89%) with a mean age ranging from 36-37 years of age per treatment group.

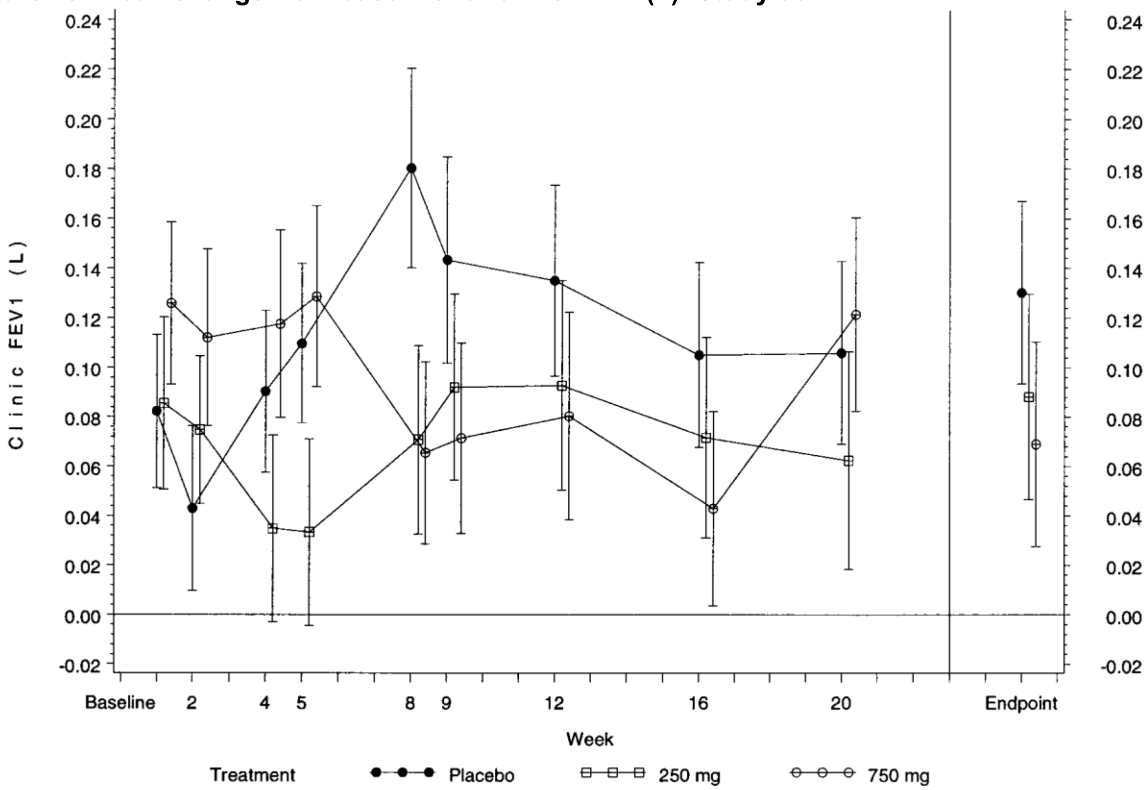
No statistically significant differences between placebo and mepolizumab treatment groups were seen for the primary endpoint. The results of the secondary endpoints, demonstrated a similar lack of treatment effect (Table 28; Figure 19). However, among the few exacerbations recorded in this study, a numeric reduction was seen for the highest evaluated dose group (750 mg IV) compared to placebo.

Table 28: Summary of efficacy data: Study 06

	Placebo N = 126	**Mepo 250 IV N = 120**	**Mepo 750 IV N = 116**
Domiciliary AM PEFR, (L/min)			
Mean change from baseline	11.32	19.03	13.08
Mean difference from placebo	--	7.83	1.70
95% CI	--	-2.89,18.55	-9.06, 12.47
Clinic pre-dose FEV1 (L)			
Mean change from baseline	0.13	0.09	0.07
Mean difference from placebo	--	-0.04	-0.05
95% CI		-0.15, 0.07	-0.16,0.05
Asthma summary symptom score[1]			
Mean change from baseline	-1.50	-1.33	-1.02
Mean difference from placebo	--	0.19	0.48
95% CI	--	-0.31, 0.70	-0.03, 0.98
Rescue medication use (puffs/day)			
Mean change from baseline	1.83	2.25	1.71
Mean difference from placebo	--	0.15	0.14
95% CI	--	-0.34,0.64	-0.36,0.63

[1] Asthma Symptom Summary Score = composite score of asthma symptoms during night, morning and daytime ranked on a 0 – 4 scale. Symptoms were recorded twice daily in the daily diary, in the am nighttime and morning scores were recorded, and evening scores were recorded in the pm.
Source: CSR Study 06 Tables 23, 25, 28 29

Figure 19: Mean change from baseline for clinic FEV1 (L): Study 06



Source: CSR Study 06 Figure 3

6 Review of Safety

Safety Summary

The safety database from this clinical development program includes data from the three pivotal efficacy and safety studies (Studies 97, 88 and 75) as well as longer-term safety data from two open-label extension studies (Studies 61 and 66) which were on-going at the time of BLA submission.

There were three (3) respiratory-related deaths in the clinical development program. However, the deaths are balanced across treatment arms (including placebo), and there is no corresponding increase in respiratory or asthma SAEs. Review of the asthma SAE data reveals a consistent imbalance in favor of mepolizumab treatment which supports the positive exacerbation treatment effect demonstrated in the clinical development program. The number of respiratory-related deaths in the program may be indicative of the underlying severity of the studied population; however, no firm conclusions can be drawn from these limited data.

An imbalance in cardiac-related SAEs is seen from evaluation of the safety data from Study 97. However, when the data are grouped into ischemic versus arrhythmogenic events, the imbalance decreases. Furthermore, no imbalance is seen in Studies 88 and 75, although these studies were of shorter treatment duration than Study 97.

While lingering concerns remain of the risk of mepolizumab use and parasitic disease, no major safety findings were observed in the data. A discussion and vote on the overall safety data is requested of the committee.

6.1 Methods

6.1.1 Studies/Clinical Studies Used to Evaluate Safety

This safety review primarily relies on data from three placebo-controlled studies in a severe asthma population: MEA112997 (Study 97), MEA115588 (Study 88) and MEA115575 (Study 75) as these studies most closely approximate the patient population to receive mepolizumab in the clinical practice. Within this review, the pooled database for these studies is referred to as the Placebo-Controlled Severe Asthma Studies (PCSA).

Longer term safety data are provided by two open-label studies, MEA115666 (Study 66), MEA115661 (Study 61). These studies were ongoing at the time of the BLA submission with updated data provided to the Division in a 120-day safety update. The data from this safety update used a cutoff date of October 27, 2014 and provides cumulative review of the data for the studies ongoing at the time of BLA submission[25].

Additional information on the sponsor's pooled analyses may be found in Section 6.1.3 of this review.

6.1.2 Categorization of Adverse Events

In the mepolizumab clinical development program an adverse event (AE) was defined as any untoward medical occurrence in a subject temporally associated with use of mepolizumab regardless of relatedness to mepolizumab. Adverse events were coded and grouped using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

[25] Data from the ongoing compassionate use program in Hypereosinophilic Syndrome provides additional deaths and non-fatal SAEs from September 2013 through October 27, 2014 as opposed to cumulative results from the study.

6.1.3 Pooling of Data Across Studies/Clinical Studies to Estimate and Compare Incidence

In addition to the PCSA database, the applicant provided multiple additional pooled safety analyses in this BLA application. The data groupings are summarized in Table 29.

Table 29: Pooled safety databases

Data Grouping	Included Indications	Number of Studies	Number of subjects
All Studies	All indications	19	2,331
Placebo-controlled Multi-dose Studies (PC)	All indications	9	1,876
Placebo-controlled Multi-dose Asthma Studies (PCMDA)	Asthma	6	1,737
Placebo-controlled Severe Asthma Studies (PCSA)[1]	Asthma	3	1,327
Open-label Extension Studies (OLE)[2]	Asthma	2	998

[1] includes data from Studies 97, 88, and 75
[2] includes data from Studies 61 and 66
Source: Modified from ISS Table 1

As noted in Section 6.1.1, this review focuses on the PCSA database as these data most closely approximate the patient population to receive this product in clinical practice. Additional long-term safety data are provided by the open-label extension (OLE) studies in severe asthma. To supplement its database, the sponsor also provided safety data from completed studies in other patient populations. These data are presented throughout this safety review where relevant.

For the review of adverse event data, many areas of this safety review focus on the exposure-adjusted analysis as opposed to frequency tables. Use of the exposure-adjusted data allows for a comparison of all active treatment arms while adjusting for the different treatment durations evaluated in each pivotal severe asthma study.

6.2 Adequacy of Safety Assessments

6.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The size of the database and duration of exposure are adequate for review. A total of 2,331 patients are included in the sponsor's overall safety database, of whom 2,022 received at least one dose of mepolizumab. Of these, a total of 1,327 patients with severe asthma were evaluated in the PCSA database with 915 receiving at least one dose of mepolizumab.

Table 30: Extent of Exposure: PCSA

		Mepolizumab				
	Placebo N = 412	**100 SC N = 263**	**75 IV N = 344**	**250 IV N = 152**	**750 IV N = 156**	**All doses**
Total # of subjects, n	412	1018	344	152	156	1299
Total subject years	284	147	254	142	144	687
Exposure (months)						
Mean	8.3	6.7	8.9	11.2	11.0	9.0
Median	7.5	7.4	7.6	12.0	12.0	7.6
Min, Max	1, 13	1, 8	1, 13	1, 13	1, 14	1, 14
Range of Exposure (months)						
< 12, n (%)	288 (70)	263 (100)	217 (63)	22 (14)	26 (17)	528 (58)
> 12, n (%)	124 (30)	0	127 (37)	130 (86)	130 (83)	387 (42)

Source: Modified from ISS Tables 3, 6

No differences in baseline demographics are seen between treatment groups. Demographic data for Studies 97, 88, and 75 are summarized in Table 7,Table 8, Table 9 respectively in Section 5.1.2.

The safety data contained in the 120-day safety update provide open-label data for mepolizumab 100 mg SC for greater than one year in 836 subjects with a median exposure of 20 months in Study 66 and 12 months in Study 61[26]. Study 61 enrolled subjects from Study 97 with a minimum 12 month break in therapy between the two studies, while Study 66 directly enrolled subjects from Studies 88 and 75 without a break in therapy providing for a greater duration of sustained exposure.

6.2.2 Explorations for Dose Response

Doses ranging from 75 mg IV up to 750 mg IV were evaluated in the mepolizumab severe asthma program. A single subcutaneous dose, 100 mg SC (the dose proposed for marketing) was evaluated in the development program. Based on PK/PD bridging data from Study 92, the systemic exposure from this dose is within the evaluated

[26] The duration of exposure from the start of the parent study into the extension study was calculated as above when there was *no break* in treatment between the two studies.

intravenous dosing. The safety data from all evaluated doses are presented and analyzed throughout the safety review to provide contextual information for the 100 mg SC dose.

6.2.3 Evaluation for Potential Adverse Events for Similar Biologics in Biologics Class

There are no monoclonal antibodies targeting IL-5 approved for use in the United States or other foreign countries. However, based on targeted pathway and preliminary safety data from Study 97, the following Adverse Events of Special Interest were pre-specified for analysis and review in this program. Because mepolizumab is a monoclonal antibody, the sponsor included evaluations of systemic and local site reactions, neoplasms, and opportunistic infections. Cardiac disorders were also specified as AESI based on preliminary safety information obtained from Study 97. Each of these AESI is discussed further in Section 6.3.4.

- Systemic reactions
- Local site reactions
- All infections including opportunistic infections
- Neoplasms
- Cardiac disorders.

6.3 Major Safety Results

6.3.1 Deaths

A total of 6 deaths were reported in the severe asthma studies: 5 in the PCSA database and one in an open label extension study. The deaths are balanced across treatment arms with 2 in placebo treated subjects, 1 in the 100 mg SC dose group, 2 in the 250 mg IV dose group, and 1 in the 750 mg dose group. Additional details of these deaths are provided in Table 31.

Table 31: Details of on-treatment deaths

Treatment	Study (Country)	Age/Sex	Cause of death Preferred Term	Additional notes
Placebo	88 *(Korea)*	51 yo/M	Road traffic accident	--

Treatment	Study (Country)	Age/Sex	Cause of death Preferred Term	Additional notes
Placebo	75 *(Germany)*	38 yo/F	GI hemorrhage and aspiration	Hospitalized for a severe asthma exacerbation and was found to have pulmonary mycoides that was treated with voriconazole. Subject then developed GI hemorrhage and aspiration leading to death
250 mg IV	97 *(Chile)*	60 yo/F	Acute pancreatitis Septic shock	Subject had biliary microlithiasis and mesenteric thrombosis. Subject then developed acute pancreatitis with an abscess followed by septic shock and death.
250 mg IV	97 *(France)*	56 yo/F	Asthma	Rapid evolution of asthma symptoms occurring over minutes. Symptoms began hours after last injection of mepolizumab. Subject was in cardiac arrest upon arrival to ER.
750 mg IV	97 *(Chile)*	54 yo/M	Asphyxia	Completed suicide No prior history of depression but also taking cyclobenzaprine
100 mg SC	OLE *(Australia)*	29 yo/M	Respiratory Arrest	Severe asthma exacerbation

The number of potential respiratory-related deaths (3 patients) in this relatively small database is notable given that deaths are not frequently seen in asthma clinical development programs. To place these data in context, GSK recently reported blinded results from its ongoing large LABA safety study in 11,724 adult and adolescent subjects with asthma. Per GSK's reports, there have been no deaths independently adjudicated as related to asthma in this large database[27]. However, it should be noted that the patient population enrolled in the large LABA safety trial differs in severity from the population evaluated in this program.

While the number of respiratory-related deaths in this program is unexpected, the data do not strongly suggest a treatment-related effect as the events are balanced across treatment arms. Reassuringly, similar concerns are not seen from a review of the non-fatal SAE data which favored treatment and demonstrated a reduction in asthma SAEs

[27] Joint Meeting of the Pulmonary Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting, March 19, 2015. Slide A-12 GSK slide set and Slide 14 FDA Introductory Remarks.

in mepolizumab treated subjects compared to placebo. The frequency of death in this clinical development program may be due to the underlying severity of the patient population evaluated in this program, although this cannot be confirmed.

In addition to the respiratory-related deaths, the death due to suicide is also of interest, particularly as the subject did not have a history of depression or prior suicide attempts. However, no conclusions for causality to mepolizumab can be drawn from this single case which is further confounded by the concomitant use of cyclobenzaprine. The post marketing section of the U.S. prescribing information for cyclobenzaprine notes that cases of depressed mood have been reported with cyclobenzaprine use as well as additional neuropsychiatric events including: abnormal sensations, anxiety, agitation, psychosis, abnormal thinking and dreaming[28]. Reassuringly, no additional non-fatal SAEs concerning for depression or neuropsychiatric events are seen from a review of the PCSA database.

6.3.2 Nonfatal Serious Adverse Events

In the PCSA database, a total of 155 subjects reported SAEs.

An imbalance in respiratory SOC favoring active treatment is seen. This imbalance is primarily driven by events of asthma, which are not unexpected in an asthma development program. The imbalance in favor of treatment is consistent with the positive treatment effect on exacerbations that mepolizumab demonstrates in this clinical development program (Table 32, Table 33).

Treatment related imbalances are seen in the Cardiac Disorders and Vascular Disorders SOC. These imbalances are discussed in greater detail in Section 6.3.5 of this review. No other consistent treatment related imbalances are seen from a review of the data.

Table 32: Exposure-adjusted[1] non-fatal SAEs by System Organ Class: PCSA

		Mepolizumab			
	Placebo 284 SY	**100 SC 147 SY**	**75 IV 254 SY**	**250 IV 142 SY**	**750 IV 144 SY**
Respiratory, thoracic, mediastinal d/o	200.7	61.0	98.3	112.5	76.7
Infections & Infestations	49.3	54.2	31.5	21.1	48.8
Injury Poisoning Procedural	17.6	6.8	15.7	14.1	7.0

[28] Flexeril (cyclobenzaprine) US Prescribing information website http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017821s051lbl.pdf accessed on January 22, 2015

		Mepolizumab			
	Placebo 284 SY	100 SC 147 SY	75 IV 254 SY	250 IV 142 SY	750 IV 144 SY
Complication					
Renal and Urinary d/o	24.6	13.6	0	14.1	0
Cardiac d/o	3.5	6.8	11.8	7.0	27.9
Gastrointestinal d/o	7.0	6.8	3.9	14.1	7.0
Nervous System d/o	14.1	0	3.9	0	7.0
Vascular d/o	0	0	11.8	7.0	7.0
Musculoskeletal and connective tissue d/o	7.0	13.6	0	0	0
Immune system d/o	3.5	6.8	3.9	0	0
Metabolism and nutrition	0	6.8	7.9	0	0
Neoplasms benign, malignant, and unspecified	7.0	0	0	7.0	0
Reproductive system and breast d/o	3.5	0	0	7.0	7.0
Skin and subcutaneous tissue d/o	0	6.8	3.9	7.0	0
General d/o and administration site conditions	0	0	3.9	7.0	0
Hepatobiliary disorders	0	6.8	3.9	0	0
Investigations	3.5	0	0	7.0	0
Blood and lymphatic system d/o	0	0	0	7.0	0
Congenital, familial, and genetic d/o	3.5	0	0	0	0
Pregnancy, puerperium and perinatal conditions	0	0	3.9	0	0
Psychiatric d/o	3.5	0	0	0	0

[1] reported as frequency per 1000 subject years SY = subject years
Source: ISS Table 2.057

Table 33: Exposure-adjusted[1] non-fatal SAEs by Preferred Term occurring in more than one subject: PCSA

		Mepolizumab			
	Placebo 284 SY	100 SC 147 SY	75 IV 254 SY	250 IV 142 SY	750 IV 144 SY
Any SAE	348.6	189.9	204.5	232.1	188.1
Asthma	193.7	61.0	94.4	112.5	76.7
Pneumonia	10.6	6.8	3.9	0	13.9
Nephrolithiasis	10.6	6.8	0	0	0
Bronchitis	7.0	0	3.9	0	0
Lobar pneumonia	3.5	0	7.9	0	0
Tendon rupture	3.5	0	3.9	0	7.0
Atrial flutter	3.5	6.8	0	0	0
Cerebrovascular accident	7.0	0	0	0	0

		Mepolizumab			
	Placebo 284 SY	100 SC 147 SY	75 IV 254 SY	250 IV 142 SY	750 IV 144 SY
Herpes zoster	0	13.6	0	0	0
Hypersensitivity	3.5	6.8	0	0	0
Hypertension	0	0	3.9	0	7.0
Myocardial ischemia	0	0	3.9	0	7.0
Viral upper respiratory tract infection	3.5	0	3.9	0	0

[1] reported as frequency per 1000 patient years SY = subject years
Source: ISS Table 17

No new safety signals are seen from a review of the cumulative data from the OLE studies provided in the 120-day safety update. Data for the AESI from the OLE are provided in Section 6.3.4.

6.3.3 Dropouts and/or Discontinuations

In the PCSA database there were a total of 35 subjects who reported an AE that led to withdrawal. No new safety concerns are seen from a review of these data. Asthma was the most frequently reported PT which is not unexpected given the underlying patient population. This occurred with greatest exposure-adjusted incidence in the 750 mg IV and placebo arms (Table 34).

Table 34: Adverse events occurring in ≥ 1 subject leading to discontinuation of mepolizumab or study withdrawal: PCSA database

		Mepolizumab			
	Placebo	100 SC	75 IV	250 IV	750 IV
Preferred term, n (%)					
N	412	263	344	152	156
Any event	12 (3)	3(1)	4(1)	8(5)	8(5)
Asthma	3 (<1)	0	1(<1)	1(<1)	2(1)
Hypersensitivity	2 (<1)	0	0	1 (<1)	2 (1)
Arthralgia	0	0	1 (<1)	1(<1)	0
Liver function test abnormal	1 (<1)	0	1 (<1)	0	0
Exposure-adjusted rates[1]					
Subject years	284	147	254	142	144
Any	45.8	20.3	19.7	70.3	55.7
Asthma	10.6	0	3.9	7.0	13.9
Hypersensitivity	7.0	0	0	7.0	13.9
Arthralgia	0	0	3.9	7.0	0
Liver function	3.5	0	3.5	0	0

		Mepolizumab			
	Placebo	100 SC	75 IV	250 IV	750 IV
test abnormal					
[1]frequency of event per 1000 subject-years of exposure SY = subject years Source: ISS Table 19					

6.3.4 Submission Specific Primary Safety Concerns

Cardiovascular Safety
The sponsor's review of the safety data from Study 97 identified an increase in SAEs within the cardiac SOC particularly for the high dose intravenous mepolizumab group (Placebo = 3[2]; 75 mg IV = 4 [3]; 250 mg IV = 2[1]; 750 mg IV (4 [3])

Given this potential signal, GSK implemented a prospective cardiovascular (CV) monitoring strategy for the remainder of its mepolizumab clinical development program. This included:

- Baseline collection of CV risk factors/functional status
- Base evaluation of clinical symptoms of ischemic heart disease (if clinically indicated)
- Additional ECG monitoring
- Use of CV-specific data collection forms to collect additional data on CV events of interest
- Use of an Independent Data Monitoring Committee (IDMC) and external adjudication panel to review CV safety. The committee adjudicated pre-specified CV events and all cause events that occurred during Phase 3 studies.

The charter for the IDMC specified that the committee would meet for the first time after 8 subjects experienced an adjudicated CV event in Studies 75 and 88. At the time of the BLA submission, this threshold was not met. A total of three events from Study 88 were adjudicated as CV or all-cause deaths (placebo: case of DVT/PE and an all-cause death from road traffic accident; mepolizumab 75 mg IV: myocardial infarction/unstable angina). No events from Study 75 met criteria for adjudication. The committee concluded at the end of the two double-blind studies that there were too few overall CV events for a meaningful assessment and recommended continuation of the open label extension studies.

In addition to the individual study results from Study 97, it is useful to consider pooled data from the placebo-controlled safety database. The SAE data were retrospectively reviewed by GSK to identify SAEs of Cardiac, Vascular, and Thromboembolic origin. This reviewer performed a similar analysis of all SAE PTs, the results of which were consistent with that reported by GSK. The exposure-adjusted data for the PCSA database are presented in Table 35. No major differences are observed when evaluating the data in subjects with or at risk for cardiovascular disease (data not shown). While decreased, a dose-dependent trend for cardiovascular events is still seen with the intravenous dosing, particularly for the high dose 750 mg IV group in the total population as well as in those with a CV history. This imbalance compared to placebo is not seen with the dose proposed for marketing. These data should be interpreted cautiously given the infrequency with which the events occurred.

Table 35: Exposure-adjusted on-treatment serious cardiac, vascular and thromboembolic events: PCSA database

			Mepolizumab							
	Placebo 284 SY		100 SC 147 SY		75 IV 254 SY		250 IV 142 SY		750 IV 144 SY	
	#	rate	#	rate	#	Rate	#	Rate	#	rate
Any event	3	10.6	1	6.8	6	23.6	3	21.1	5	34.8
Cardiac d/o										
Any event	1	3.5	1	6.8	3	11.8	1	7.0	4	27.9
Atrial flutter	1	3.5	1	6.8	0	0	0	0	0	0
Myocardial ischemia	0	0	0	0	1	3.9	0	0	1	7.0
Acute myocardial infarction	0	0	0	0	1	3.9	0	0	0	0
Atrial fibrillation	0	0	0	0	0	0	0	0	1	7.0
Coronary artery insufficiency	0	0	0	0	0	0	1	7.0	0	0
Coronary artery thrombosis	0	0	0	0	1	3.9	0	0	0	0
Myocardial infarction	0	0	0	0	0	0	0	0	1	7.0
SVT	0	0	0	0	0	0	0	0	1	7.0
Vascular d/o										
Any event	0	0	0	0	3	11.8	1	7.0	1	7.0
Hypertension	0	0	0	0	1	3.9	0	0	1	7.0
Distributive shock	0	0	0	0	0	0	1	7.0	0	0
Malignant hypertension	0	0	0	0	1	3.9	0	0	0	0
Venous thrombosis limb	0	0	0	0	1	3.9	0	0	0	0
Nervous system d/o										
Any event	2	7.0	0	0	0	0	0	0	0	0
Cerebrovascular accident	2	7.0	0	0	0	0	0	0	0	0
Gastrointestinal d/o										
Any event	0	0	0	0	0	0	1	7.0	0	0

			Mepolizumab							
	Placebo 284 SY		100 SC 147 SY		75 IV 254 SY		250 IV 142 SY		750 IV 144 SY	
Thrombosis mesenteric vessel	0	0	0	0	0	0	1	7.0	0	0

[1]frequency of event per 1000 subject-years of exposure SY = subject year
Source: Response to information request dated February 2, 2015 Table 2.203

When the data are categorized into ischemic events vs. arrhythmic events, the imbalance decreases further (Table 36) making it difficult to conclude that the data demonstrate a treatment-related cardiovascular effect.

Table 36: Serious ischemic and arrhythmic adverse events: PCSA database

		Mepolizumab			
	Placebo N = 412	100 SC N = 263	75 IV N = 344	250 IV N = 152	750 IV N = 156
Serious ischemic events*	2 (<1)	0	3 (1)	2 (1)	2 (1)
Serious arrhythmic events+	1 (<1)	1 (<1)	0	0	2 (1)

* PTs include: myocardial ischemia, acute myocardial infarction, coronary artery thrombosis, myocardial infarction, cerebrovascular accident , thrombosis mesenteric vessel
+ PTs include: atrial flutter, atrial fibrillation, supraventricular tachycardia
Source: Response to information request dated February 2, 2015 reviewer modifications of Table 2.204 and reviewer modifications of Table 2.203

A total of 14 cases of Serious Cardiac, Vascular, Thromboembolic and Ischemic AEs were reported from the OLE studies through October 27, 2014 (Table 37). The lack of a placebo comparator arm makes interpretation of these data difficult; however, an increased frequency of events compared to the placebo-controlled database is not seen. Of these 14 events, six events were sent to the CEC for adjudication. A total of 4 events were confirmed as CV events (Table 37). The fatal event was adjudicated by the charter but was not CV-related (respiratory arrest, see Section 6.3.1 Table 31).

Table 37: Serious Cardiac, Vascular, Thromboembolic, and Ischemic Adverse Events: OLE Studies 61 and 66[1]

	Mepo 100 SC		
	Study 66 N = 347	Study 61 N = 651	Total N = 998
Any Event, n (%)	5 (1)	9 (1)	14 (1)
Atrial fibrillation	1 (<1)	3 (<1)	4 (<1)
Acute myocardial infarction[2]	1 (<1)	0	1 (<1)
Angina pectoris[2]	0	1 (<1)	1 (<1)
Cardio-respiratory arrest	0	1 (<1)	1 (<1)
Cerebral hemorrhage	0	1 (<1)	1 (<1)
DVT	0	1 (<1)	1 (<1)
Hypertension	1 (<1)	0	1 (<1)
Hypertensive heart disease	0	1 (<1)	1 (<1)
Hypotension	0	1 (<1)	1 (<1)
Mitral Valve incompetence	0	1 (<1)	1 (<1)
Myocardial infarction[2]	0	1 (<1)	1 (<1)
Pulmonary embolism [2]	0	1 (<1)	1 (<1)
Subarachnoid hemorrhage	1 (<1)	0	1 (<1)
Thrombophlebitis superficial	1 (<1)	0	1 (<1)
Serious ischemic events	1 (<1)	3 (<1)	4(<1)

Source: 120 day safety update March 3 2015 Modified from Tables 17, 18, Table 2.044
[1] cumulative data through October 27, 2014
[2] classified as serious ischemic events

Table 38: Adjudication committee interpretation of cardiac events

	Mepo 100 SC		
Adjudication Category	Preferred Term	Study 66 N = 651	Study 61 N = 998
Myocardial infarction/unstable angina requiring hospitalization	Acute myocardial infarction	1	0
	Myocardial infarction	0	1
Stroke	Subarachnoid hemorrhage	1	0
Deep vein thrombosis/pulmonary embolism	Deep vein thrombosis	0	1
All cause death	Respiratory arrest	1	0

Source: 120 day safety update March 3, 2015 Tables 19

Hypersensitivity reactions, anaphylaxis and local injection site reactions

A treatment-related imbalance in local injection site reactions is seen from a review of the data in the PCSA database (Table 39). The data from the OLE studies did not reveal an increased frequency of hypersensitivity events in patients receiving mepolizumab 100 mg SC.

Table 39: On-treatment systemic and local injection site reactions: PCSA

		Mepolizumab			
	Placebo N = 412	**100 SC N = 263**	**75 IV N = 344**	**250 IV N = 152**	**750 IV N = 156**
Systemic Hypersensitivity Reaction	7(2)	3(1)	4(1)	3(2)	2(1)
Local Site Reactions	14(3)	21(8)	11(3)	0	0
Source: ISS Table 2.086, 2.179					

This mepolizumab development program used the NIAID/FAAN anaphylaxis criteria[29] to evaluate potential cases of systemic hypersensitivity reactions to determine if the cases were anaphylaxis. In addition, the applicant conducted a retrospective manual review of the associated symptoms outlined in the anaphylaxis criteria, a retrospective standard MedDRA Query (SMQ) for anaphylactic reactions, and a review of AEs associated with eczema/rash, dyspnea, and nasal congestion to determine if reporting of these events was associated with unrecognized hypersensitivity reactions.

A review of the line listings for hypersensitivity events was also conducted by this reviewer. No cases meeting the NIAID/FAAN criteria were identified by this review of the PCSA database or OLE Studies 97 or 88. However, one potential anaphylactic case from the ongoing open-label Study 201312 was identified. Study 201312 is an open-label extension of Study 61, enrolling subjects with a history of life-threatening/seriously debilitating asthma. Details of this case are outlined below.

- Study 201312: 42-year-old female with a history of sulfite allergy (previous reactions to red wine) developed itching, angioedema and bronchospasm 30 min after ingestion of 100 g of raisins and 14 hours after her most recent dose of mepolizumab. Examination at the ER revealed oxygen saturation of 94% (baseline value), normal blood pressure, and no evidence of soft tissue swelling or urticaria although wheezing was audible. The subject was treated with clemastine, bronchodilator nebulizers and prednisone. The case narrative notes that no changes were made to the mepolizumab dosing. However, information regarding re-challenge is not available as the event occurred just prior to the database lock on October 27, 2014[30].

[29] Sampson et al., “Second symposium on the definition and management of: a summary report.” J Allergy Clin Immunol 2006; 117:391-7.
[30] Hypersensitivity event and most recent dose of mepolizumab were both recorded on September 16, 2014.

While this reviewer concurs with the investigator's assessment that the comorbid condition of a sulfite allergy is the more likely cause for this event, a delayed reaction to mepolizumab cannot be ruled out at this time.

Infections including opportunistic Infections

Herpes zoster is the only opportunistic infection to occur in more than one subject in the PCSA database. The PT of Herpes Zoster occurred in 4 subjects treated with mepolizumab 75 mg IV, 2 subjects each in the placebo and mepo100 mg SC treatment groups, and a case of ophthalmic herpes zoster in the 750 mg IV dose group (Table 40). The OLE studies include an additional 5 reports of herpes zoster through the October 27, 2014 safety cutoff date in patients treated with mepolizumab 100 mg SC and review of the data from the Hypereosinophilic development program reveals additional cases. While chronic corticosteroid use may be a confounder, the imbalance between treatment and placebo arms in the PCSA database is suggestive of a treatment-related effect.

The OLE studies also include 3 reports of esophageal candidiasis through the October 27, 2014 safety cutoff date. Interpretation of these data is limited by the lack of a placebo comparator arms for these studies, and further confounded by background inhaled corticosteroid use which is a known risk factor for the development of esophageal candidiasis.

Of note, the clinical development program excluded enrollment of patients with parasitic disease. However, there was one report of parasitic gastroenteritis that was treated with albendazole in a subject receiving mepolizumab 100 mg SC in Study 88 (no confirmatory diagnostic testing was performed). There were no reports of parasitic infection from the OLE studies. Conclusions regarding the use of mepolizumab in parasitic disease cannot be drawn from the data provided in the clinical development program, and further evaluation of this issue may be warranted given the mechanism of action of this biologic.

Table 40: Opportunistic infections: PCSA database

		Mepolizumab			
	Placebo N = 412	100 SC N = 263	75 IV N = 344	250 IV N = 152	750 IV N = 156
Any event	4 (<1)	3 (1)	4 (1)	0	2(1)
Herpes zoster	2 (<1)	2 (<1)	4 (1)	0	0
Blastomycosis	1 (<1)	0	0	0	0
Gastrointestinal fungal infection	0	1(<1)	0	0	0
Ophthalmic herpes simplex	1 (<1)	0	0	0	1 (<1)
Respiratory moniliasis	0	0	0	0	1 (<1)

		Mepolizumab			
	Placebo N = 412	100 SC N = 263	75 IV N = 344	250 IV N = 152	750 IV N = 156
Source: ISS Table 2.123					

No imbalance in infectious SAEs is noted in this clinical development program; see Section 6.3.2, Table 32 and Table 33 for additional information.

Malignancies

There are no treatment-related imbalances in the malignancy data from the PCSA database. A total of 3 malignancies were reported in the placebo-treated subjects, 1 subject in the mepolizumab 75 mg IV group and 1 subject in the 250 mg IV dose group (Table 41).

In the OLE studies, there were 10 reports of malignancies through the October 27, 2014 safety cutoff date. These included 2 reports of breast cancer, 2 reports of prostate cancer, 1 basal cell carcinoma, 1 colon adenoma, 1 endometrial cancer, 1 gastric cancer, 1 skin cancer, and 1 squamous cell carcinoma.

The reported malignancies from this development program are not uncommon in the general population.

Table 41: On- treatment malignancy: PCSA

		Mepolizumab			
	Placebo N = 412	100 SC N = 263	75 IV N = 344	250 IV N = 152	750 IV N = 156
Any event	3 (<1)	0	1 (<1)	1(<1)	0
Basal cell carcinoma	0	0	1 (<1)	0	0
Basosquamous carcinoma	1 (<1)	0	0	0	0
Prostate cancer	1 (<1)	0	0	0	0
Squamous cell carcinoma	1 (<1)	0	0	0	0
Uterine cancer	0	0	0	0	1 (<1)
Source: ISS Table 2.116					

6.4 Supportive Safety Results

6.4.1 Common Adverse Events

In the section of this review, common adverse events are defined as events occurring in ≥ 3% of subjects in a given treatment group. On-treatment adverse events occurring more frequently in the 100 mg SC dose and route proposed for marketing than placebo are provided in Table 42.

Table 42: Common on-treatment Adverse Events reported by 3% of more of subjects in any treatment group and more frequent in the mepolizumab 100 mg SC arm: Study MEA115575 and first 24 weeks of MEA115588

	Placebo N = 257	**Mepo 100 SC N = 263**
Preferred Term, n %		
Headache	46 (18)	51 (19)
Injection site reaction	8 (3)	20 (8)
Back pain	9 (4)	14 (5)
Fatigue	11 (4)	12 (5)
Influenza	6 (2)	7 (3)
Urinary tract infection	4 (2)	9 (3)
Abdominal pain upper	5 (2)	7 (3)
Pruritus	5 (2)	7 (3)
Eczema	1 (<1)	9 (3)
Muscle spasms	1 (<1)	7 (3)
Source: Response to IR dated February 2, 2015 Table 2.202		

No major differences are seen from a review of the common adverse events from all the doses included in the PCSA database or the OLE studies through the October 27, 2014 safety cutoff date.

6.4.2 Laboratory Findings

No clinically meaningful differences in chemistry parameters are noted for the mepolizumab 100 mg SC compared to placebo (data not shown). A dose dependent trend for increased transaminases is seen with the intravenous dosing, particularly for the high dose 750 mg IV group (Table 43). Of note, no associated trend in increased bilirubin is seen from these data and review of the AE data does not reveal an imbalance in liver adverse events. In addition, no imbalance is seen with the dose proposed for marketing. One additional subject with elevated transaminases and an SAE of cholestatic jaundice was reported in the 120-day safety update; however, the subject continued on mepolizumab treatment and the event resolved.

Decreased eosinophil counts are seen in the mepolizumab treated groups; however, this is an expected effect of the biologic. No additional clinically meaningful differences in hematologic parameters are seen from a review of the data (data not shown).

Table 43: Summary of LFTs above upper limit normal: PCSA

		Mepolizumab			
	Placebo N = 412	Mepo 100 SC N = 263	Mepo 75 IV N = 344	Mepo 250 IV N = 152	Mepo 750 IV N =156
ALT					
> 2x ULN	6 (1)	4 (2)	4 (1)	0	4 (3)
> 3x ULN	3 (<1)	0	3 (<1)	1 (<1)	2 (1)
AST					
> 2x ULN	4 (<1)	2 (<1)	2 (<1)	1 (<1)	3 (2)
> 3x ULN	2 (<1)	1 (<1)	3 (<1)	0	3 (2)
AP					
> 2x ULN	0	0	0	0	0
> 3x ULN	0	0	0	0	0
Bilirubin[1]					
> 2xULN	0	0	0	0	0
> 3x ULN	0	0	0	0	0
GGT					
> 2x ULN	14 (3)	9 (3)	16 (5)	6 (4)	7 (4)
> 3x ULN	17 (4)	6 (2)	15 (4)	6 (4)	9 (6)

[1] if direct bilirubin is available, then it must be > 35% total bilirubin to satisfy criteria
Source: ISS Table 2.145

6.4.3 Vital Signs

Vital sign data, including the absolute change and mean change from baseline data for Study 97 and absolute change data from Studies 88 and 75 were reviewed. No clinically significant differences between treatment groups are seen for sitting pulse, systolic, or diastolic blood pressures.

6.4.4 Electrocardiograms (ECGs)

ECGS were assessed at Week 20 and Week 56 (or early withdrawal visit) in Study 97. They were assessed at Week 8, 16, 24, and 4 weeks post-dose for subjects entering the OLE studies and 12 weeks post-last dose for subjects not continuing into the OLE studies for Studies 88 and 75.

In general, monoclonal antibodies are not associated with QTc prolongation and thorough QTc studies are generally not required for these clinical development programs. For the mepolizumab programs, a few outlier subjects had maximum post-baseline QTc(F) values > 480 and ≤ 500 msec; however, causality to the investigational product cannot be given the limited number of outlier subjects. The effects on heart rate are discussed in Section 6.4.3.

The ECGs in this program were evaluated by licensed cardiologists and categorized as abnormal or normal for the three efficacy studies. For Studies 75 and 88, the findings were further classified as “abnormal, clinically significant” or abnormal, “not clinically significant”. No major treatment-related imbalances are seen from a review of these data.

6.4.5 Immunogenicity

As mepolizumab is a monoclonal antibody, anti-mepolizumab antibodies with an assessment of neutralizing antibody status for positive values, was assessed throughout this clinical development program. No immunogenicity concerns from a clinical perspective are raised from a review of the immunogenicity data.

6.5 Other Safety Explorations

6.5.1 Biologic-Demographic Interactions

No new safety signals are identified by evaluating the safety data by gender, age, race, ethnicity, and region. However, the subgroup analyses by age and race are limited by the small sample sizes in each of these categories.

6.5.2 Biologic-Disease Interactions

Mepolizumab was evaluated in subjects with less severe asthma in Study 06. Additional details of this study design and the efficacy data can be found in Section 5.1.7 of this document. While the study was relatively small, the safety data from this study allow for estimation of mepolizumab’s safety profile in a less severe asthmatic population.

No major differences in the safety profile are demonstrated by a review of the safety data from Study 06; although, the analysis is limited by the small sample size.

Rates of adverse events were comparable between placebo and mepolizumab treatment groups with a slight numeric imbalance in favor of treatment (placebo 76%; mepolizumab 250 and 750 68% and 69% respectively). The most common AE preferred term was URTI (18-20%) followed by asthma. For the AE term of asthma a small numeric imbalance in favor of treatment (placebo 24%; mepolizumab 250 mg IV 21% and mepolizumab 750 mg IV 17%) was seen. There were no deaths during the study. Non-fatal SAEs were reported in the 4 subjects in the placebo group (vertigo, bladder carcinoma, unintended pregnancy, asthma), in three subjects in the mepolizumab 250 mg dose group (hydrocephalous, constipation, and GI disorder NOS) and in two subjects in the mepolizumab 750 mg dose group (2 reports of asthma).

Clinical Pharmacology Briefing Document for the Pulmonary—Allergy Drugs Advisory Committee Meeting

June 11, 2015

Nucala (mepolizumab for injection)
BLA 125526

Dose: 100 mg subcutaneous injection every 4 weeks

Proposed indication:
"Add–on maintenance treatment in patients 12 years and older with severe eosinophilic asthma identified by blood eosinophils ≥ 150 cells/μL at initiation of treatment or ≥ 300 cells/μL in the past 12 months. Nucala has been shown to reduce exacerbations of asthma in patients with an exacerbation history"

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2.2 Clinical Pharmacology

2.2.1 Background

Nucala (mepolizumab) is a humanized monoclonal anti-IL5 antibody. IL-5 is a cytokine important in the growth, differentiation, activation and survival of eosinophils. Mepolizumab is proposed for add-on maintenance treatment in patients aged 12 years and older with severe eosinophilic asthma identified by blood eosinophils greater than or equal to 150 cells/μL at initiation of treatment or blood eosinophils greater than or equal to 300 cells/μL in the past 12 months. Mepolizumab is supplied as 100 mg lyophilized powder per vial to be reconstituted with 1.2 mL sterile water for Injection. The proposed dosing regimen is 100 mg subcutaneous injection once every 4 weeks.

2.2.2 Biopharmaceutics

Three mepolizumab drug product (DP) presentations have been used throughout the clinical development program. The pilot product (50 mg/vial and 250 mg/vial) was used in the pre-clinical and Phase I clinical studies. Mepolizumab drug product 1 (MDP1, 250 mg/vial) was used in a Phase IIa Clinical Pharmacology study (MEA114092), three pivotal Phase III clinical studies (MEA112997, MEA115588, MEA115575) as well as for initiation of the open-label (OLE) studies (MEA115666, and MEA115661). Mepolizumab drug product 2 (MDP2, 100 mg/vial) is used in all ongoing clinical studies, including the two OLE safety studies (MEA115661 and MEA115666). MDP2 is the proposed commercial presentation of the product. Excipient quantities and manufacturing process were different between the pilot product and the MDP1/2. However, no clinical PK/PD bridging study was conducted between the pilot product and the MDP1/2. Between MDP1 and MDP2, the DP composition was the same.

2.2.3 Pharmacokinetics

Pharmacokinetics in Healthy Subjects

The PK of MDP1 in healthy subjects was evaluated in Study MEA115705. Four groups of eight subjects were randomized 3:1 to receive mepolizumab IV (10, 75, 250 and 750 mg) or placebo. Following a 30-minute IV infusion, mepolizumab plasma concentrations declined in a bi-exponential manner. Over the dose range 10–750 mg, mepolizumab showed linear and dose-proportional PK. The mean terminal-phase elimination half-life was 20 to 36 days.

Pharmacokinetics in Patients

Four studies were conducted to evaluate the PK of MDP1 in patients with asthma (MEA114092, MEA112997, MEA115588, and MEA115575). Sparse pharmacokinetic samples were collected throughout, and analyzed using population PK methods.

In Study MEA115588, the systemic exposure of mepolizumab was comparable between 75 mg IV and 100 mg SC every 4 weeks, and the estimated bioavailability was 80% for 100 mg SC injection in subjects with severe asthma. Following SC administration of 100 mg mepolizumab in asthmatic subjects, the mean volume of distribution was 63 to 82 mL/kg, the mean clearance ranged from 4.0 to 4.7 mL/day/kg, and the mean elimination half-life (t1/2) was 3 to 4 weeks.

Pharmacokinetics in Special Populations

The effect of sex, age, race, and body weight on the PK of mepolizumab was assessed using the population approach, in which Study MEA115588 was included for the population PK analysis.

Race, Gender, Age, and Weight
Race, ethnicity, age and gender did not significantly impact the PK of mepolizumab. Mepolizumab clearance increased with body weight.

Immunogenicity

In the two Phase 3 studies MEA115588 and MEA115575, a total of 15 (6%) subjects treated with 100 mg mepolizumab SC were positive for post-baseline anti-mepolizumab antibodies. Antibodies were mostly transient, with 50% of antibody positive subjects demonstrating only one positive test results. Antibody titers were generally low. One subject developed neutralizing antibodies after mepolizumab exposure; no SAEs were associated with this case. There was about 22% numerical increase of mepolizumab clearance in post-baseline antibody-positive patients following 100 mg mepolizumab SC administration.

2.2.4 Pharmacodynamics

Study 114092 was a Phase 2 study that evaluated the PK/PD relationship between the exposure of subcutaneously administered mepolizumab (12.5 mg, 125 mg and 250 mg SC) and different PD markers of response. The study also compared PK/PD profiles between three SC treatments and one IV treatment (75 mg IV).

The investigation was a multi-center, open-label, randomized, dose-ranging, four-parallel-group study in adult asthmatic subjects with elevated blood eosinophil levels (≥200 cells /µL in according to protocol amendment 1). Three doses were given for each treatment group and the dosing interval was 4 weeks. A total of 66 subjects completed the study.

Enrolled subjects were males or females aged 18 to 65 years, who showed evidence of airway reversibility (FEV1 ≥12%) within 30 minutes of inhalation of albuterol or airway hyperresponsiveness documented in the 12 months prior to randomization. Subjects' FEV1 values were ≥45% and <90 % of predicted normal value during screening. Subjects were required to be on a stable dose of an inhaled corticosteroid or combination (ISC and LABA) therapy for at least 12 weeks prior to screening.

The major PD results from study 114092 and other studies are presented below. In general, 75 mg IV and 125 mg, and 100 mg SC mepolizumab demonstrate a similar reduction effect in blood eosinophil counts in Studies 114092 and MEA115588.

Blood Eosinophil Count

A dose-dependent reduction in blood eosinophil counts was observed from Study 114092 (Figure 1). The absolute mean values of blood eosinophil counts reduced maximally to 64 /μL, 249 /μL, 71 μL, and 52 /μL (or reduced by 82%, 57%, 85%, and 91% from the baseline) for 75 mg IV, 12.5 mg SC, 125 mg SC, and 250 mg SC groups, respectively. A greater than two thirds reduction in eosinophil counts was observed starting 3 days after the first dose of 75 mg IV, 125 mg SC, and 250 mg SC mepolizumab. The average maximal reduction was seen around Week 8.

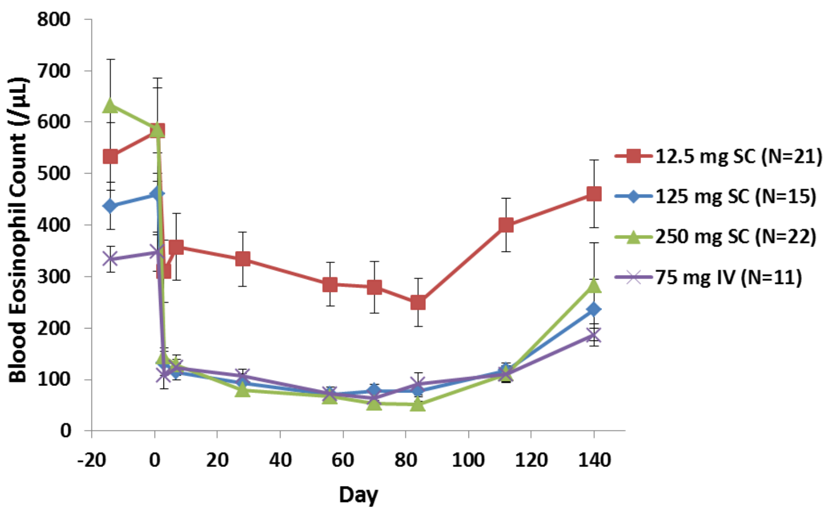

Figure 1: Mean (± SE) absolute blood eosinophil count-time profiles following 75 mg IV, 12.5 mg SC, 125 mg SC, and 250 mg SC mepolizumab once every 4-week treatment in study 114092. Total three doses were given with dosing interval of 4 weeks. Source: adapted from CSR 114092, Figure 1

The blood eosinophil-reduction effect was comparable between mepolizumab 75 mg IV and 100 mg SC treatment in Study 115588. The absolute mean values of blood eosinophil counts reduced maximally to 50 /μL and 40 /μL (reduced by 82% and 86% from the baseline) for 75 mg IV, and 100 mg SC treatment group, respectively (Figure 2). On the contrary, the mean blood eosinophil counts only decreased by 25% in the placebo group. It appeared that the maximal reduction level was maintained for at least 4 weeks following 28 weeks of mepolizumab 75 mg IV or 100 mg SC dosed every 4-weeks.

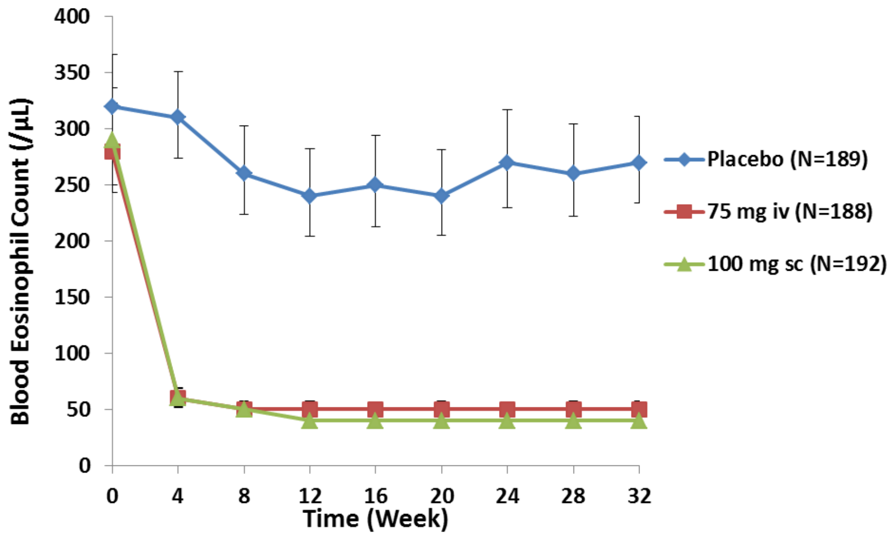

Figure 2: Mean (± SE) absolute blood eosinophil count-time profiles following placebo, 75 mg IV, and 100 mg SC mepolizumab once every 4-week treatment in study 115588. Total eight doses were given with dosing interval of 4 weeks. Source: adapted from CSR 115588, Table 6.73.

Sputum Eosinophil Count

There was a general trend towards a reduction in sputum eosinophil counts following mepolizumab treatment in Study 114092 (Figure 3). However, the sputum eosinophil counts (%) at baseline (pre-dose on Day 1) were not balanced between four active treatment groups. The largest decrease from baseline was observed in the mepolizumab 250 mg SC groups, with smaller decreases in the mepolizumab12.5 mg SC group.

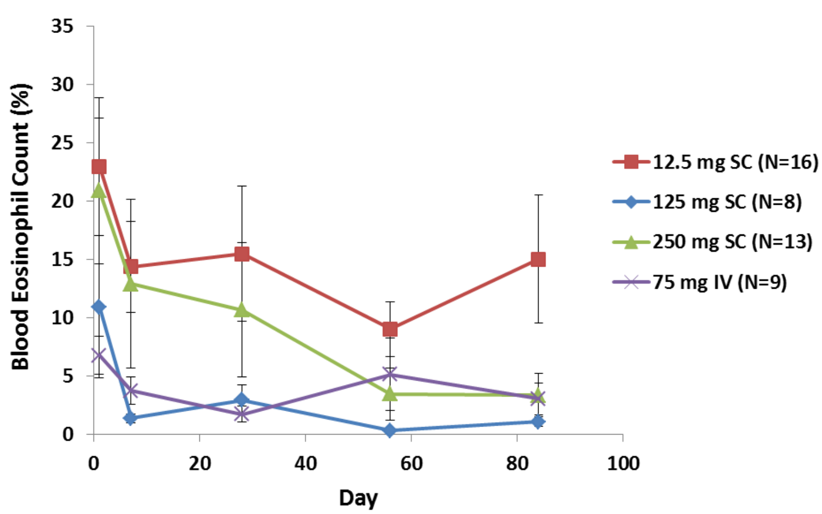

Figure 3: Mean (± SE) absolute sputum eosinophil count-time profiles following 75 mg IV, 12.5 mg SC, 125 mg SC, and 250 mg SC mepolizumab once every 4-week treatment in study 114092. Total three doses were given with dosing interval of 4 weeks. Source: from data set sputum.xpt submitted under study 114092.

Total Serum IL-5 Concentration

The serum total IL-5 pre-dose baseline concentration was usually below the limit of quantification. In a single-dose study (Study 115705), mepolizumab demonstrated a dose-dependent increase in total serum IL-5 levels over time in healthy Japanese males (Figure 4). On the other hand, free IL-5 levels were essentially undetectable throughout the study in subjects with or without mepolizumab treatment (Figure 4). However, this dose-response relationship was not clear from Study 114092 in asthmatic patients with elevated blood eosinophil levels (Figure 5).

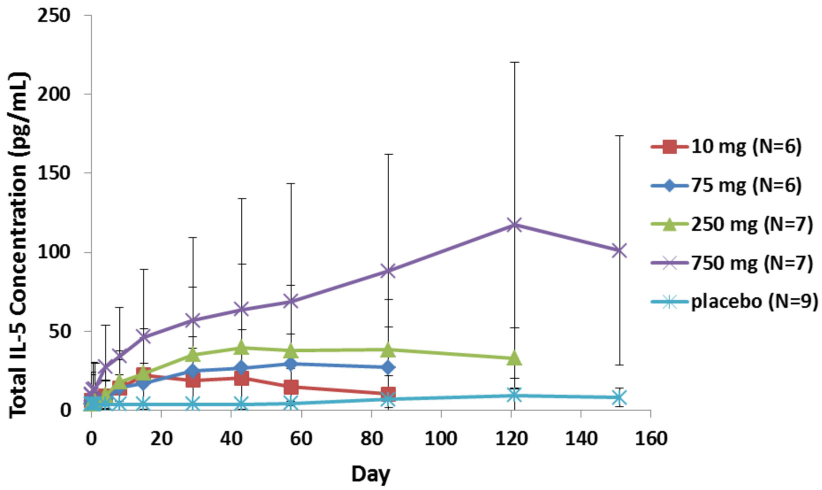

Figure 4: Mean (± SE) serum total IL-5 concentrations following single-dose administration in healthy Japanese males from Study 115705. Source: Adapted from CSR 115705, Table 14.

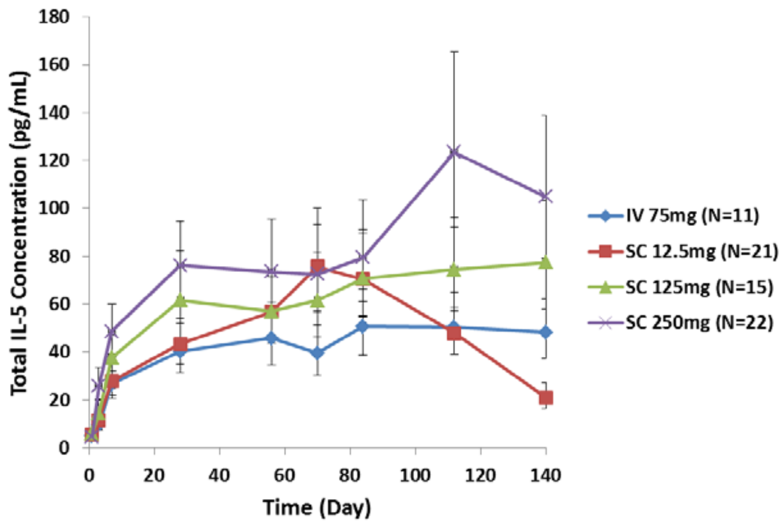

Figure 5: Mean (± SE) serum total IL-5 concentrations in asthmatic patients with elevated blood eosinophil levels from Study 114092. Total three doses were given with dosing interval of 4 weeks. Source: Adapted from CSR 114092, Figure 4.

2.2.5 Exposure-Response Relationship

Dose-response and exposure-response relationships were observed for reduction of blood eosinophil counts. The estimated dose required for 50% of maximal percentage reduction of blood eosinophil counts was 11 mg. There were no dose-response or exposure-response relationships observed for FEV1 response and exacerbation rate.